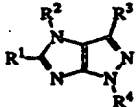
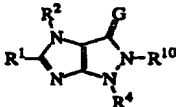


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(54) Title: NITROGEN SUBSTITUTED IMIDAZO[4,5-c]PYRAZOLES AS CORTICOTROPIN RELEASING HORMONE ANTAGONISTS			
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(II)</p> </div> </div>			
(57) Abstract  Corticotropin releasing factor (CRF) antagonists of Formulae (I) or (II), and their use in treating psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.			

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TITLE

NITROGEN SUBSTITUTED IMIDAZO[4,5-c]PYRAZOLES AS  
CORTICOTROPIN RELEASING HORMONE ANTAGONISTS.

5                   FIELD OF THE INVENTION

This invention relates to novel nitrogen substituted imidazo[4,5-c]pyrazole compounds and pharmaceutical compositions, and to methods for the treatment of psychiatric disorders and neurological  
10 diseases, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders, as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity  
15 associated with psychopathological disturbance and stress. In particular, the present invention relates to novel imidazopyrimidines and imidazopyridines, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders,  
20 neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

25

BACKGROUND OF THE INVENTION

Corticotropin releasing hormone or factor (herein referred to as CRH or CRF), a 41 amino acid peptide, is the primary physiological regulator of  
30 proopiomelanocortin(POMC) -derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland,  
35 immunohistochemical localization of CRF has

demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G.F. Koob, *Persp. Behav. Med.* 2:39 (1985); E.B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

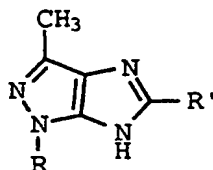
In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted

- adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].
- There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist  $\alpha$ -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et

- al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which  
5 was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].
- 10 The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is  
15 observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist ( $\alpha$ -helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects  
20 qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].
- 25 Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050, Pfizer WO 95/33750, Pfizer WO  
30 95/34563, Pfizer WO 95/33727 and Pfizer EP 778277 A1.

European Patent Application Number 190457 A1 discloses 3-methyl-imidazo [4,5-c] pyrazole derivatives which have the general formula shown  
35 below. The compounds have an intense depressant

activity on the central nervous system, including anticonvulsant, sedative, analgesic and hypothermizing.



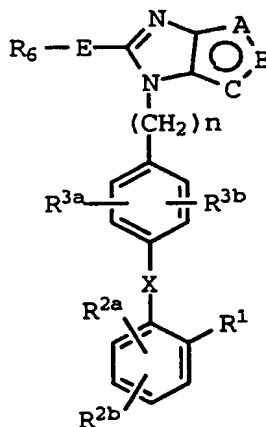
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Similar imidazo[4,5-c]pyrazole derivatives are disclosed in Tetrahedron, Vol. 46, pp. 5777-5788

10 (1990).

European Patent Application Publication Number 407102A discloses angiotensin II antagonists having the general formula:

15

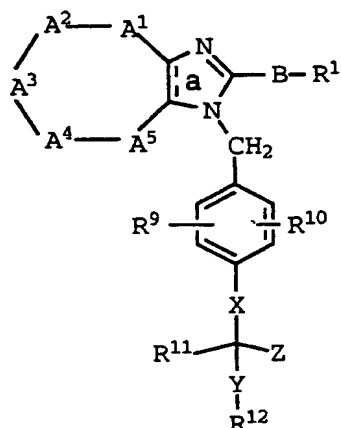


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PCT Patent Application WO 91/11999 discloses angiotensin II antagonists having the general formula

shown below. These compounds also have utility as treatments for cognitive dysfunctions, depression, anxiety and dysphoric mental states.

5



10           Insofar as is known, novel nitrogen substituted  
imidazo[4,5-c]pyrazoles, which are described in detail  
below, have not been previously reported as  
corticotropin releasing factor antagonist compounds  
useful in the treatment of psychiatric disorders and  
15   neurological diseases, including major depression,  
anxiety-related disorders, post-traumatic stress  
disorder, supranuclear palsy and feeding disorders as  
well as treatment of immunological, cardiovascular or  
heart-related diseases and colonic hypersensitivity  
20   associated with psychopathological disturbance and  
stress.

#### SUMMARY OF THE INVENTION

25           In accordance with one aspect, the present  
invention provides novel compounds which bind to



corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention provides novel compounds of formulae (I) and (II) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of formulae (I) and (II), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to

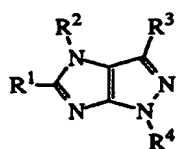
disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; 5 panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent 10 depression, child abuse induced depression, and postpartum depression; dysthemia, bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as 15 Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by 20 psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; 25 head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive 30 heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, 35 sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary

incontinence; senile dementia of the Alzheimer's type;  
 multiinfarct dementia; amyotrophic lateral sclerosis;  
 chemical dependencies and addictions (e.g.,  
 dependencies on alcohol, cocaine, heroin,  
 5 benzodiazepines, or other drugs); drug and alcohol  
 withdrawal symptoms; osteoporosis; psychosocial  
 dwarfism and hypoglycemia in mammals.

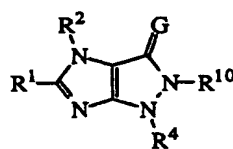
According to a still further aspect of the  
 10 invention, the compounds provided by this invention  
 (and especially labelled compounds of this invention)  
 are also useful as standards and reagents in  
 determining the ability of a potential pharmaceutical  
 to bind to the CRF receptor.  
 15

#### DETAILED DESCRIPTION OF THE INVENTION

[1] Thus, in a first embodiment, the present invention  
 20 provides novel compounds of Formulae (I) and (II):



(I)



(II)

25

or isomers thereof, stereoisomeric forms thereof, or  
 mixtures of stereoisomeric forms thereof, and  
 pharmaceutically acceptable salt forms thereof, wherein:

30 R<sup>1</sup> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub>  
 alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, where such haloalkyl is

substituted with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
C<sub>4</sub>-C<sub>8</sub> cycloalkylalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl,  
heteroaryl or heterocyclyl;

5 R<sup>2</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl,  
C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, where  
each group can be optionally substituted with 1 to  
3 substituents independently selected at each  
occurrence from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub>  
10 alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, aryl, heteroaryl,  
heterocyclyl, halogen, cyano, NR<sup>6</sup>R<sup>7</sup>, OR<sup>7</sup>, thiol,  
S(O)<sub>n</sub>R<sup>9</sup>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, OC(O)R<sup>9</sup>, NR<sup>8</sup>COR<sup>7</sup>, NR<sup>8</sup>CONR<sup>6</sup>R<sup>7</sup>,  
NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, CONR<sup>6</sup>R<sup>7</sup>;

or

15 S(O)<sub>n</sub>R<sup>9</sup>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>;

or

C<sub>1</sub>-C<sub>4</sub> haloalkyl, where C<sub>1</sub>-C<sub>4</sub> haloalkyl may be  
substituted with 1-6 halogens;

or

20 aryl or aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl or  
heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl, or  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl), wherein C<sub>1</sub>-C<sub>4</sub> alkyl in  
aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl) or  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl) is optionally substituted  
25 with substituents selected from C<sub>1</sub>-C<sub>8</sub> alkyl, COR<sup>7</sup>,  
CO<sub>2</sub>R<sup>7</sup>, S(O)<sub>n</sub>R<sup>9</sup>, cyano and aryl;

n is independently at each occurrence 0, 1, or 2;

30 R<sup>3</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-  
C<sub>6</sub> haloalkyl, where such haloalkyl is substituted

with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>2</sub>-C<sub>10</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, cyano, OR<sup>6</sup>, thiol, S(O)<sub>n</sub>R<sup>9</sup>, NR<sup>6</sup>R<sup>7</sup>, aryl, or heteroaryl;

5 R<sup>4</sup> is phenyl, pyridyl, pyrimidyl, triazinyl, furanyl, naphthyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, 2,3-dihydrobenzofuranyl, 2,3-  
10 dihydrobenzothienyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl or pyrazolyl, where each R<sup>4</sup> is attached via an unsaturated carbon atom and each R<sup>4</sup> may be optionally substituted with 1 to 4 R<sup>5</sup> groups;

15 R<sup>5</sup> is independently at each occurrence selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, where C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub>  
20 cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl are optionally substituted with 1-3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>4</sub> alkyl, nitro, halogen, cyano, NR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>COR<sup>7</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, COR<sup>7</sup>, OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>CONR<sup>6</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, thiol, or  
25 S(O)<sub>n</sub>R<sup>9</sup>;  
or  
nitro, halogen, cyano, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens, NR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>COR<sup>7</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, COR<sup>7</sup>, OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>CONR<sup>6</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>,  
30 thiol, or S(O)<sub>n</sub>R<sup>9</sup>;

R<sup>6</sup> and R<sup>7</sup> are independently at each occurrence selected from:

- (1) H;
- (2) C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, each optionally substituted with 1-6 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, cyano, nitro, OR<sup>12</sup>, thiol, S(O)<sub>n</sub>R<sup>9</sup>, COR<sup>12</sup>, CO<sub>2</sub>R<sup>12</sup>, NR<sup>8</sup>COR<sup>12</sup>, NR<sup>8</sup>CONR<sup>11</sup>R<sup>12</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, NR<sup>11</sup>R<sup>12</sup>, and CONR<sup>11</sup>R<sup>12</sup>;
- (3) aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl or heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl, or heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl;

15

R<sup>8</sup> is independently at each occurrence selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>4</sub>-C<sub>7</sub> cycloalkylalkyl;

or

20

phenyl or phenyl(C<sub>1</sub>-C<sub>4</sub> alkyl), each optionally substituted with 1-3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH;

25 R<sup>9</sup> is independently at each occurrence selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cycloalkylalkyl;

or

30 phenyl or phenyl(C<sub>1</sub>-C<sub>4</sub> alkyl), each optionally substituted with 1-3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH;

R<sup>10</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl, heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl, heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl), where C<sub>1</sub>-C<sub>4</sub> haloalkyl is optionally substituted with 1 to 6 halogens;

R<sup>11</sup> and R<sup>12</sup> are independently at each occurrence selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cycloalkylalkyl, or C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens; or phenyl or phenyl(C<sub>1</sub>-C<sub>4</sub> alkyl), each optionally substituted with 1-3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R<sup>13</sup>;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, or indazolyl, each optionally substituted with 1 to 4 substituents independently selected from at each occurrence R<sup>13</sup>;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3

substituents independently selected at each occurrence from  $R^{13}$ ;

5  $R^{13}$  is independently at each occurrence selected from  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl,  $C_3$ - $C_6$  cycloalkyl,  $C_4$ - $C_{12}$  cycloalkylalkyl, where  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl,  $C_3$ - $C_6$  cycloalkyl,  $C_4$ - $C_{12}$  cycloalkylalkyl are optionally substituted with 1-3 substituents independently  
10 selected at each occurrence from  $C_1$ - $C_4$  alkyl, nitro, halogen, cyano,  $NR^8R^9$ ,  $NR^8COR^9$ ,  $NR^8CO_2R^9$ ,  $COR^9$ ,  $OR^9$ ,  $CONR^8R^9$ ,  $NR^8CONR^8R^9$ ,  $CO_2R^9$ , thiol, or  $S(O)_nR^9$   
or  
15 nitro, halogen, cyano,  $C_1$ - $C_4$  haloalkyl optionally substituted with 1-6 halogens,  $NR^8R^9$ ,  $NR^8COR^9$ ,  $NR^8CO_2R^9$ ,  $COR^9$ ,  $OR^9$ ,  $CONR^8R^9$ ,  $NR^8CONR^8R^9$ ,  $CO_2R^9$ , thiol, or  $S(O)_nR^9$ ;

20 [2] In a preferred embodiment, the present invention provides novel compounds of Formulae (I) and (II) wherein:  $R^4$  is phenyl, pyridyl or pyrimidyl, each optionally substituted by 1 to 4  $R^5$  groups.

25 [3] In a more preferred embodiment, the present invention provides novel compounds of Formula (I) and (II), wherein:  $R^1$  is selected from H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, where such haloalkyl is substituted with 1-6 halogens,  $C_3$ - $C_6$  cycloalkyl, or aryl.

30 [4] In an even more preferred embodiment, the present invention provides novel compounds of Formulae (I) and



(II), wherein: R<sup>1</sup> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, where such haloalkyl is substituted with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or aryl and R<sup>4</sup> is phenyl, pyridyl or pyrimidyl, each optionally substituted by 1 to 4 R<sup>5</sup> groups.

[5] In an even further preferred embodiment, the present invention provides novel compounds of Formula (I) and (II), wherein the compound is selected from the group:

- 1- (2-chloro-4-trifluoromethyl)phenyl-5-ethyl-3-methyl-4-[1-(1-methyl)butane]imidazo[4,5-c]pyrazole;
- 15 1- (2-chloro-4-trifluoromethyl)phenyl-5-ethyl-4-[1-(1-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;
- 4- (n-butyl)-1- (2-chloro-4-bromo)phenyl-5-ethyl-3-methylimidazo[4,5-c]pyrazole;
- 20 1- (2-chloro-4-bromo)phenyl-5-ethyl-3-methyl-4-[1-(1-methyl)butane]imidazo[4,5-c]pyrazole;
- 1- (2-chloro-4-bromo)phenyl-5-ethyl-4-[1-(1-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;
- 25 5-ethyl-3-fluoromethyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole;
- 30 5-ethyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole;
- 1- (2,6-dichloro-4-bromo)phenyl-5-ethyl-4-[1-(1-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;

- 1- (2,4-dichloro)phenyl-5-ethyl-4- [1- (1-ethyl)butane] -3-  
methylimidazo[4,5-c]pyrazole;
- 5 1- (2,4-dichloro)phenyl-5-ethyl-3-methyl-4- [1- (1-  
methyl)butane]imidazo[4,5-c]pyrazole;
- 1- (2,4-dichloro)phenyl-5-ethyl-3-methyl-4- [1- (1,3-  
dimethyl)butane]imidazo[4,5-c]pyrazole;
- 10 1- (2,6-dichloro-4-bromo)phenyl-5-ethyl-3-methyl-4- [1- (1-  
methyl)butane]imidazo[4,5-c]pyrazole;
- 15 5-ethyl-4- [1- (1-ethyl)butane] -3-methyl-1- (2,4,5-  
trichloro)phenylimidazo[4,5-c]pyrazole;
- 5-ethyl-3-methyl-4- [1- (1-methyl)butane] -1- (2,4,5-  
trichloro)phenylimidazo[4,5-c]pyrazole;
- 20 5-ethyl-4- [1- (1-methyl)pentane] -3-methyl-1- (2,4,6-  
trichloro)phenylimidazo[4,5-c]pyrazole;
- 1- (2-bromo-4-isopropyl)phenyl-5-ethyl-4- [1- (1-  
ethyl)butane] -3-methylimidazo[4,5-c]pyrazole;
- 25 1- (2-bromo-4-isopropyl)phenyl-5-ethyl-3-methyl-4- [1- (1-  
methyl)butane]imidazo[4,5-c]pyrazole;
- 1- (2-bromo-4,6-dichloro)phenyl-5-ethyl-4- [1- (1-  
ethyl)butane] -3-methylimidazo[4,5-c]pyrazole;
- 30 1- (2-bromo-4,6-dichloro)phenyl-5-ethyl-3-methyl-4- [1- (1-  
methyl)butane]imidazo[4,5-c]pyrazole;
- 35 4- (n-butyl) -1- (2,6-dichloro-4-bromo)phenyl-5-ethyl-3-  
methylimidazo[4,5-c]pyrazole;

1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-3-methyl-4-[1-(3-methyl)butane]imidazo[4,5-c]pyrazole;

5 1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-4-[1-(2-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;

4-benzyl-1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-3-methylimidazo[4,5-c]pyrazole; and

10

1-(2,6-dichloro-4-bromo)phenyl-4-(3,4-difluorobenzyl)-5-ethyl-3-methylimidazo[4,5-c]pyrazole

or a pharmaceutically acceptable salt form thereof.

15 [6, 7, 8, 9, 10] In another preferred embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of compounds of Formulae (I) and (II).

20

[11, 12, 13, 14, 15] In yet another preferred embodiment, the present invention provides a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, 25 Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, 30 hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or 35 facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in

mammals, comprising: administering to the mammal a therapeutically effective amount of compounds of Formulae (I) and (II).

- 5           The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as
- 10 by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present
- 15 invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure
- 20 are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.
- 25           The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a
- 30 stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

          The present invention is intended to include all isotopes of atoms occurring in the present compounds.

35 Isotopes include those atoms having the same atomic

number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

- 5           When any variable (e.g.,  $R^6$ ) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2  
10  $R^6$ , then said group may optionally be substituted with up to two  $R^6$  groups and  $R^6$  at each occurrence is selected independently from the definition of  $R^6$ . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable  
15 compounds.

- When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via  
20 which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable  
25 compounds.

- As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include, but are not limited  
30 to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or  
35 more halogen (for example  $-C_vF_w$  where  $v = 1$  to  $3$  and  $w = 1$  to  $(2v+1)$ ). Examples of haloalkyl include, but are

not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5-to

7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl,

imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids (e.g., L-amino acids), modified and unusual amino acids (e.g., D-amino acids), as well as



amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Natural protein occurring amino acids include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tyrosine, tryptophan, proline, and valine. Natural non-protein amino acids include, but are not limited to arginosuccinic acid, citrulline, cysteine sulfinic acid, 3,4-dihydroxyphenylalanine, homocysteine, homoserine, ornithine, 3-monoiodotyrosine, 3,5-diiodotyrosine, 3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine,  $\beta$ -phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the

scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate  
5 with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable  
10 salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the  
15 quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric;  
20 and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric,  
25 toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by  
30 conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally,  
35 nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of

suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

- 5        Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended
- 10    to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such
- 15    prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound.
- 20    Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it
- 25    cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

- "Stable compound" and "stable structure" are meant
- 30    to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

- "Substituted" is intended to indicate that one or
- 35    more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from

the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit HIV infection or treat the symptoms of HIV infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of HIV replication) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

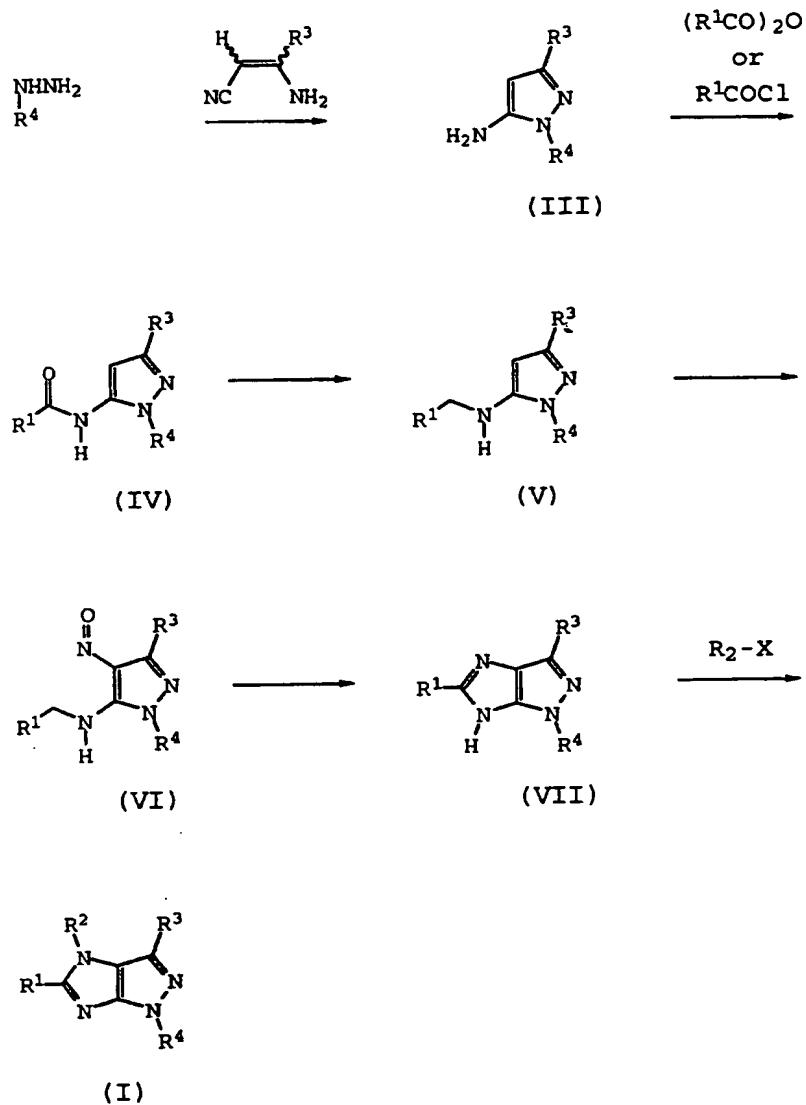
The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

### Synthesis

The novel substituted bicyclic imidazo[4,5-c]pyrazoles of Formulae (I) and (II) of this invention can be prepared by one of the general schemes outlined below, in particular Schemes 1-2.

Compounds of Formula (I) of this invention may be prepared as shown in Scheme 1.

SCHEME 1



An appropriate hydrazine ( $\text{R}^4\text{NHNH}_2$ ), either as the free base or as the corresponding mineral acid salt, may be condensed with acrylonitrile compounds of formula  $\text{R}^3(\text{NH}_2)\text{C}=\text{C}(\text{CN})\text{H}$  to afford pyrazole compounds of formula

(III). These cyclizations are preferably conducted in aqueous media and at elevated temperatures up to boiling. When  $R^3$  is hydrogen, 2-halogenoacrylonitrile compounds of formula  $CH_2=CH(CN)Hal$  or 2,3-dihalogenopropionitrile compounds of formula  $Hal'CH_2CH(CN)Hal$  may be cyclized with the hydrazines of formula  $R^4NHNH_2$ . Hal and Hal' may be independently selected from chlorine, bromine or iodine. One skilled in the art of heterocyclic chemistry will readily understand the optimal combinations of conversions necessary to prepare a number of compounds of formula (III) with  $R^3$  and  $R^4$  variations and can refer to the review of Potts, K.T. (*Comprehensive Heterocyclic Chemistry*, Katritzky, A.R., et.al., Eds., Pergamon Press, Oxford, 1984, 5, pg. 111-157) or Vicentini, et.al. (*Tetrahedron*, 1990, 46, 5777).

Compounds of formula (III) may be readily condensed with compounds of formula  $(R^1CO)_2O$  or  $R^1COCl$  to provide amides of formula (IV). The condensations may be conducted neat or in the optional presence of cosolvent. The reactions are preferably run at room temperature where  $R^1$  is methyl and at elevated temperature up to the boiling point of the anhydride or cosolvent used where  $R^1$  is larger than methyl. Amides of formula (IV) may then be converted, in the presence of a reducing agent, to the substituted amino pyrazoles of formula (V). Reducing agents include, but are not limited to, lithium aluminum hydride and borane. Reactions are generally run in ethereal solvents, for example tetrahydrofuran and diethyl ether. The reductions are carried out for a period of time between 1 hour and 4 days, and at room temperature or elevated temperature up to reflux in order to effect the reaction. If borane is used, it may be employed as a complex, for example, but not limited

to, borane-methyl sulfide complex, borane-piperidine complex, borane-pyridine complex, and borane-tetrahydrofuran complex.

- 5 In preparation for ring closure to the imidazole, compounds of formula (V) may be nitrosated in the presence of acid and a suitable nitrosating agent such as, but not limited to, isoamyl nitrite in an alcoholic solvent such as methanol, ethanol, or isopropanol. The reactions are generally conducted at room temperature and afford compounds of formula (VI) in high yield and  
10 purity after filtration or column chromatography. Cyclization to imidazopyrazoles of formula (VII) may be accomplished by refluxing precursors of formula (VI) in the presence of a base such as, but not limited to,  
15 pyridine or other non-nucleophilic organic base for a period of time between 1 hour and 3 days and at a temperature ranging from room temperature up to the boiling point of the base or co-solvent employed. Cosolvents such as, but not limited to, tetrahydrofuran  
20 may be used, however, it may be preferable to conduct the cyclizations in the absence of cosolvent. Compounds of formula (VII) are expected to exist as a mixture of imidazole tautomers, and one skilled in the art will immediately recognize this.
- 25 Finally, treatment of compounds of formula (VII) with a base and a compound of formula  $R^2-X$  wherein X represents a leaving group may afford the desired imidazopyrazole compounds of formula (I). Leaving groups may include, but are not limited to, bromo,  
30 chloro, iodo, cyano, alkoxy, methanesulfonyl, and p-toluenesulfonyl. Possible bases include, but are not limited to, the sodium, lithium or potassium bis(trimethylsilyl)amides, sodium or potassium hydride, alkyl lithiums and alkyl grignards and inorganic bases  
35 such as sodium, potassium and lithium hydroxide. The

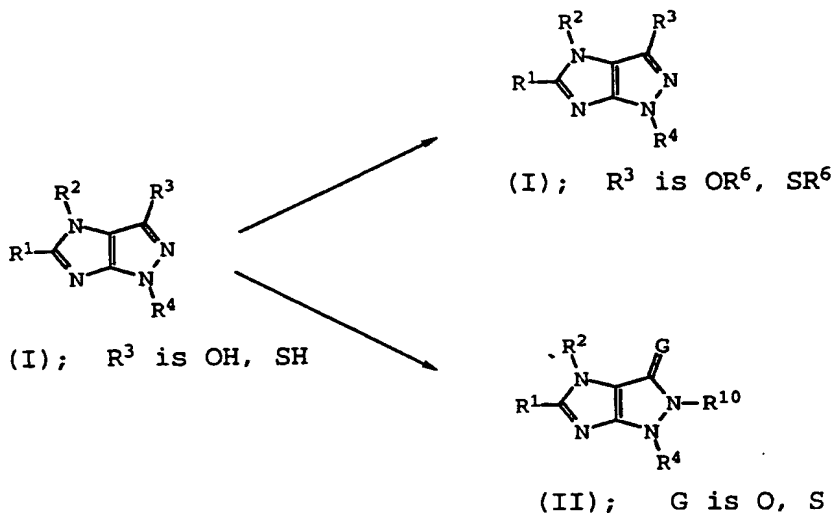
reactions are optionally conducted at room temperature or at elevated temperatures up to the boiling point of a cosolvent. A wide variety of inert solvents may be employed, for example, dimethylformamide, 5 dimethylsulfoxide, toluene, tetrahydrofuran, diethyl ether, and methylene chloride. The reactions may be successfully performed in glass reaction vessels or polypropylene wells, and one skilled in the art of organic chemistry will readily understand the optimal 10 combinations of above conditions for effecting this transformation, or can consult the text of Larock, R.C. (*Comprehensive Organic Transformations*, VCH Publishers, New York, 1989). Although regiomerization alkylation products are conceivably possible from tautomers of 15 formula (VII), the experimental conditions taught herein will selectively provide the desired regiomers represented by compounds of formula (I).

Alternatively, compounds of formula (I) may be formed from compounds of formula (VII) by treatment with 20 a base and subsequent addition to the carbon-carbon double bond of an  $\alpha,\beta$ -unsaturated carboxylic acid derivative, ketone, aldehyde, or nitrile; a process commonly accepted as the Michael reaction. Bases and optional inert cosolvents may be selected from those 25 identified (*vide supra*). One skilled in the art of organic synthesis will readily appreciate the utility of the Michael reaction, and may consult the teachings of House, H.O. (*Modern Synthetic Reactions*, W.A. Benjamin, Inc., Menlo Park, CA., 1972, p 595).

30 As shown in Scheme 2, compounds of formula (I) where  $R^3$  is OH or SH may be transformed into compounds of formula (I) where  $R^3$  is  $OR^6$  or  $SR^6$  or compounds of formula (II) where G is O or S and the pyrazole nitrogen is substituted as  $R^{10}$ .



## SCHEME 2



- Reactions to afford compounds of formula (I) where  $R^3$  is  $OR^6$  or  $SR^6$  may be preferably conducted with oxophilic alkylating agents such as, but not limited to, the trialkyloxonium tetrafluoroborates and/or thiophilic alkylating agents such as, but not limited to, dialkyl sulfates. Reactions to afford compounds of formula (II), where G is O or S and the pyrazole nitrogen is substituted (Scheme 2) as  $R^{10}$  are more preferably effected by treatment of compounds of formula (I,  $R^3$  is OH or SH) with a base such as, but not limited to, potassium hydroxide in a solvent such as acetone or other inert solvent with a reagent  $R^{10}-X$  where X is a leaving group (*vide supra*). These product compounds arise via the tautomeric nature of compounds of formula (I) where  $R^3$  is OH or SH.

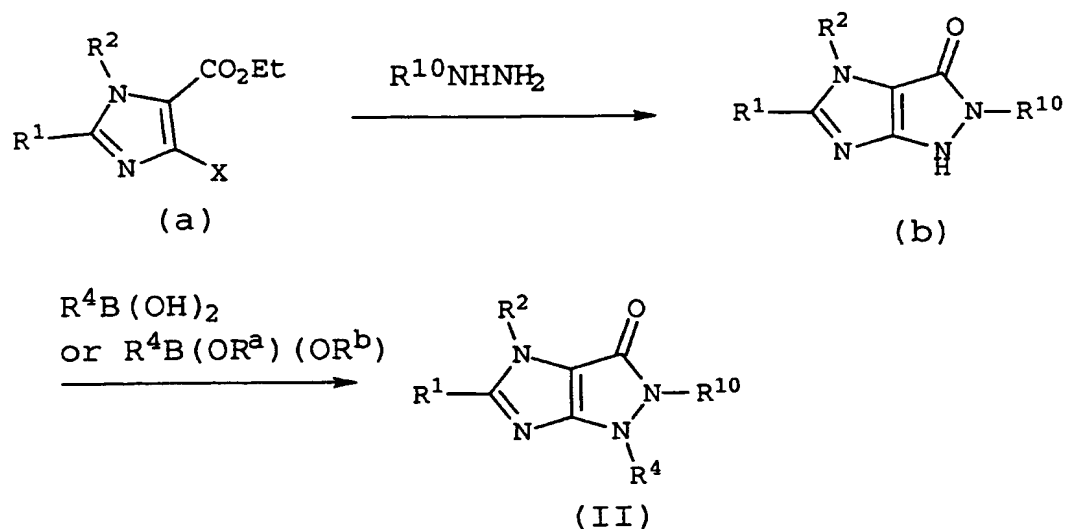
In the described manner then, the novel substituted bicyclic imidazo[4,5-c]pyrazoles of formula (I) and (II)

of this invention can be prepared by one of the general schemes outlined above. See Schemes 1-2.

Compounds of Formula (II) may also be prepared as outlined in Scheme 3.

5

## SCHEME 3



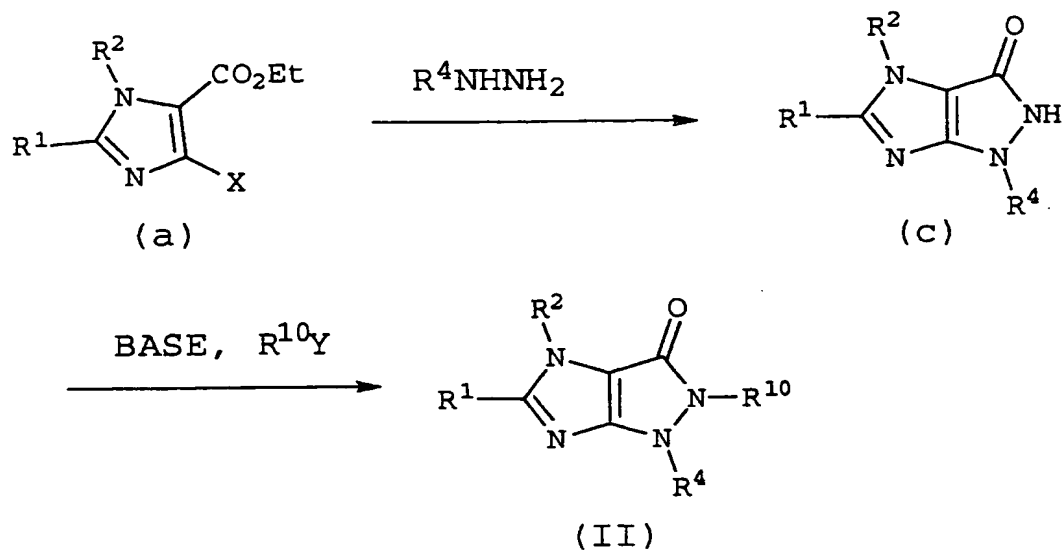
- Imidazoles of Formula (a) (where  $X$  = halogen,  $NH_2$ ,  
 alkylamino (1-6 carbons), dialkylamino (2 - 12 carbons),  
 10 alkylthio (1 to 6 carbons) or alkylsulfonyl (1 to 6  
 carbons) may be reacted with a compound of the formula  
 $R^{10}NHNH_2$ , in the presence or absence of a base, in an  
 inert solvent to give intermediates of formula (b).  
 Bases may include, but are not limited to, alkali metal  
 15 hydrides (preferably sodium hydride), alkali metal  
 alkoxides (1 to 6 carbons) (preferably sodium methoxide  
 or sodium ethoxide), alkaline earth metal hydrides,  
 alkali metal dialkylamides (preferably lithium di-  
 isopropylamide), alkali metal bis(trialkylsilyl)amides  
 20 (preferably sodium bis(trimethylsilyl)amide), trialkyl

- amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably
- 5 acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-
- 10 methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20 to 100°C.
- 15 Intermediates (b) may then be treated with a boronic acid or a boronic acid ester of the formula  $R^4B(OH)_2$  or  $R^4B(OR^a)(OR^b)$  (where  $R^a$  and  $R^b$  are lower alkyl (1 to 6 carbons) or together  $R^a$  and  $R^b$  are lower
- 20 alkylene (2 to 12 carbons) in the presence of a metal catalyst with or without a base in an inert solvent to give compounds of Formula (II). Metal catalysts include, but are not limited to salts or phosphine complexes of Cu, Pd or Ni (e.g.  $Cu(OAc)_2$ ,  $PdCl_2(PPh_3)_2$ ,  $NiCl_2(PPh_3)_2$ ). Bases may include, but are not limited
- 25 to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1
- 30 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably
- 35 N,N-di-isopropyl-N-ethyl amine or triethylamine) or

aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 150°C.

Alternatively, compounds of Formula (II) may be prepared as outlined in Scheme 4.

## SCHEME 4



Imidazoles of Formula (a) (where X is defined above) may be treated with compounds of the formula  $R^4NHNH_2$  to yield intermediates (c) in the presence or absence of a base in an inert solvent. Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from  $-80^\circ\text{C}$  to  $150^\circ\text{C}$ .

Intermediates (c) may then be treated with a reagent of the Formula  $R^{10}X$  to give compounds of Formula (II) in the presence or absence of a base in an inert solvent. Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali

metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 150°C.

25

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

35

Example 1

**Preparation of 4-Cyclopropylmethyl-3,5-dimethyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole:**

5        Step A:  $\beta$ -Aminocrotononitrile (14.68 g, 0.18 mol) was dissolved in 1.0N HCl (500 ml) and treated with 2,4,6-trichlorophenylhydrazine (36 g, 0.17 mol). The reaction was refluxed 4h, cooled, and decanted into a 2 liter beaker. The solution was diluted with water (250  
10 ml) and neutralized with 10% NaOH. The resultant precipitate was filtered and dried to constant weight to afford 44.71 g (95%) of the desired aminopyrazole as a white crystalline solid, mp 135.5-136.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (s, 2H), 5.50 (s, 1H), 3.48 (bs, 2H),  
15 2.25 (s, 3H). Anal. Calcd. for  $\text{C}_{10}\text{H}_8\text{N}_3\text{Cl}_3$ : C, 43.43; H, 2.92, N, 15.19. Found: C, 43.56; H, 2.92; N, 15.09.

Step B: The product from Part A (14.0 g, 0.05 mol) was suspended in acetic anhydride (40 ml) and allowed to  
20 stir at room temperature. The reaction became homogeneous after 20 minutes and was stirred 40 additional minutes, then transferred to a slurry of ice (600 ml). The resultant precipitate was stirred 1h, filtered and dried to constant weight, affording 14.22 g  
25 (88%) of acetylated product, mp 210.0-211.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (s, 2H), 6.81 (bs, 1H), 6.47 (s, 1H), 2.33 (s, 3H), 2.08 (s, 3H). Anal. Calcd. for  $\text{C}_{12}\text{H}_{10}\text{N}_3\text{Cl}_3\text{O}_1$ : C, 45.24; H, 3.16; N, 13.19. Found: C, 45.52; H, 3.18; N, 13.10.

30        Step C: The product from Part B (16.63 g, 0.05 mmol) was dissolved in dry tetrahydrofuran (100 ml) under an atmosphere of nitrogen, and treated with borane/THF complex (156 ml, 0.15 mol) via addition

funnel. Upon completion of addition, the reaction was brought to reflux for 48 hours. The reaction was cooled, treated with 10% NaOH (100 ml), and stirred 1h. The heterogeneous mixture was diluted with water (400 ml) and diethyl ether (350 ml) and transferred to a separatory funnel. The mixture was partitioned and the aqueous layer reextracted with diethyl ether (2 X 100 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated in-vacuo. Column chromatography on silica gel (450 g), eluting with hexanes/ethyl acetate (2/1) afforded the substituted amino pyrazole, 5.89 g (c. 40%) as a white crystalline solid, mp 81.5-83.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.47 (s, 2H), 5.38 (s, 1H), 3.14 (m, 2H), 3.03 (bs, 1H), 2.26 (s, 3H), 1.19 (t, 3H, J=7.0 Hz). Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>3</sub>Cl<sub>3</sub>: C, 47.32; H, 3.97; N, 13.80. Found: C, 47.41; H, 4.01; N, 13.56.

Step D: The product from Step C (7.78 g, 25.54 mmol) was dissolved in ethanol (100 ml), cooled to 0°C, and treated with 1.0N HCl (0.5 ml) and isoamyl nitrite (3.42 ml, 25.54 mmol). The reaction was stirred 5 hours before final concentration in-vacuo to remove solvent. Purification via column chromatography (600 g) eluting with hexanes/ethyl acetate (1/2) yielded a violet crystalline solid, 7.14 g (87%), mp 180.0-181.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.50 (s, 2H), 2.84 (m, 2H), 2.73 (s, 3H), 1.14 (t, 3H, J=7.3 Hz). Anal. Calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>4</sub>Cl<sub>3</sub>O<sub>1</sub>: C, 43.20; H, 3.32; N, 16.79. Found: C, 43.06; H, 3.26; N, 16.54.

Part E: The product from Part D (7.82 g, 0.023 mol) was dissolved in pyridine (50 ml) and the homogeneous solution refluxed 8 hours. The reaction was concentrated in-vacuo to remove pyridine and purified via column chromatography (600 g) eluting initially with



ethyl acetate/hexanes (1/2) and then with ethyl acetate to afford desired imidazopyrazole, 1.71 g (c. 25%), mp 245°C (dec.). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.20 (bs, 1H), 7.42 (s, 2H), 2.52 (s, 3H), 2.44 (s, 3H). MS (CI)

5 M+H=315.

Part F: The product from Part E (0.10 g, 0.32 mmol) was charged to a dry flask, dissolved in anhydrous dimethylformamide (5.0 ml), and treated with sodium hydride (0.03 g, 0.70 mmol). After stirring 5 minutes, 10 the crimson reaction was quenched with cyclopropylmethylbromide (77 µl, 0.80 mmol). The reaction was heated to 100°C and allowed to stir 30 minutes, whereupon the reaction returned to a golden yellow color. After dilution with water (30 ml) the 15 reaction was extracted with ethyl acetate (4 X 15 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in-vacuo*. Purification on silica gel (30 g) eluting with ethyl acetate/hexanes (2/1) gave 50.3 mg of the title 20 compound, mp 190.0-192.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 (s, 2H), 3.94 (d, 2H, J=7.5 Hz), 2.52 (s, 3H), 2.50 (s, 3H), 1.26 (m, 1H), 0.71 (m, 2H), 0.40 (m, 2H). HRMS calcd. for M+H (C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>Cl<sub>3</sub>): 369.0441. Found: 369.0446.

25

### Example 3

#### **Preparation of 3,5-Dimethyl-4-[1-(2-ethyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole:**

30 The product from Example 1, Part E (61 mg, 0.19 mmol) was reacted with sodium hydride (19 mg, 0.48 mmol) and 1-bromo-2-ethylbutane (108 µl, 0.77 mmol) in dimethylformamide (2.0 ml) as described for the

preparation of Example 1, Part F. Title compound: mp  
112.0-114.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 2H),  
3.89 (d, 2H, J=7.3 Hz), 2.51 (s, 3H), 2.48 (s, 3H), 1.8  
(m, 1H), 1.39 (m, 4H), 0.95 (m, 6H). HRMS calcd. for  
5 M+H (C<sub>18</sub>H<sub>22</sub>N<sub>4</sub>Cl<sub>3</sub>): 399.0910. Found: 399.0896.

Examples 2 and 4-9 given in TABLE 1 may be prepared  
in the same manner as described for the preparation of  
Examples 1 and 3, starting with the product from Example  
10 1, Part E and substituting the appropriate electrophile.

#### Example 11

##### **Preparation of 4-Benzyl-3,5-dimethyl-1-(2,4,6-trimethylphenylimidazo[4,5-c]pyrazole:**

15 Step A: β-Aminocrotononitrile (11.96 g, 0.15 mol)  
was dissolved in 1.0N HCl (350 ml) and treated with  
2,4,6-trimethylphenylhydrazine, hydrochloride (25.89 g,  
0.14 mol). The reaction was refluxed 4h, cooled, and  
decanted into a 2 liter beaker. The solution was  
20 diluted with water (250 ml) and neutralized with 10%  
NaOH. The resultant precipitate was filtered and dried  
to constant weight to afford 27.82 g (93%) of the  
desired aminopyrazole as a white crystalline solid, mp  
127-129°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.93 (s, 2H), 5.42 (s, 1H),  
25 3.4 (bs, 2H), 2.31 (s, 3H), 2.23 (s, 3H), 2.02 (s, 6H).

Step B: The product from Part A (10.0 g, 46.40  
mmol) was suspended in acetic anhydride (35 ml) and  
allowed to stir at room temperature. The reaction  
became homogeneous after 20 minutes and was stirred 40  
30 additional minutes, then transferred to a slurry of ice  
(500 ml). The resultant precipitate was stirred 2h,  
filtered and dried to constant weight, affording 8.14 g  
(68%) of acetylated product, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.98 (s,

2H), 6.78 (bs, 1H), 6.52 (s, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 2.04 (s, 3H), 1.96 (s, 6H).

Step C: The product from Step B (8.1 g, 31.47 mmol) was dissolved in anhydrous THF (80 ml) and treated with lithium aluminum hydride (63 ml, 62.94 mmol, 1.0 M/THF) under nitrogen at room temperature. The reaction was stirred 1.5 h at room temperature and 1.0 h at 50°C, and quenched by the addition of 10% sodium hydroxide (10 ml). The heterogeneous slurry was filtered through celite with copious diethyl ether washings. The filtrate was concentrated *in-vacuo* and purified by column chromatography on silica gel (250 g), eluting with hexanes/ethyl acetate (1/1) to provide the desired product, 7.3 g (95%) as a crystalline solid.

Step D: The product from Step C (7.3 g, 29.99 mmol) was dissolved in ethanol (50 ml), cooled to 0°C, and treated with 1.0 N HCl (14 drops) and isoamyl nitrite (4.02 ml, 29.99 mmol). The reaction was stirred 10 minutes, warmed to room temperature, and stirred an additional 5 hours. The reaction was concentrated *in-vacuo* to remove ethanol and purified by column chromatography on silica gel (600 g) eluting with hexanes/ethyl acetate (2/1) to afford a violet crystalline solid, 7.14 g (87%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.95 (bs, 1H), 6.94 (s, 2H), 2.70 (s, 3H), 2.69 (q, 2H, J=7.2 Hz), 2.33 (s, 3H), 2.10 (s, 6H), 1.03 (t, 3H, J=7.3 Hz).

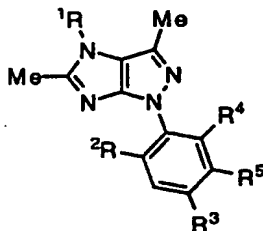
Step E: The product from Step D (7.14 g, 26.21 mmol) was dissolved in anhydrous pyridine (50 ml) and brought to reflux for 8 hours. The reaction was then concentrated *in-vacuo* to dryness and directly purified by column chromatography on silica gel (600 g) eluting with ethyl acetate/hexanes (2/1) to afford a dark solid, 1.24 g (19%), mp 191-193°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.54 (bs,

1H), 6.87 (s, 2H), 2.39 (s, 3), 2.38 (s, 3H), 2.27 (s, 3H), 1.99 (s, 6H).

Step F: The product from Part E (0.125 g, 0.49 mmol) was charged to a dry flask, dissolved in anhydrous dimethylformamide (7.0 ml), and treated with sodium hydride (0.05 g, 1.22 mmol). After stirring 30 minutes, the dark reaction was quenched with benzylbromide (234  $\mu$ l, 1.96 mmol). The reaction was heated to 50°C and allowed to stir 1 hour, whereupon the reaction returned to a golden yellow color. After dilution with water (40 ml) the reaction was extracted with ethyl acetate (4 X 15 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in-vacuo*. Purification on silica gel (40 g) eluting with ethyl acetate/hexanes (1/1) gave 83.8 mg (50%) of the title compound, mp 88-89°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.4 (m, 3H), 7.15 (d, 2H, J=8.0 Hz), 6.90 (s, 2H), 5.24 (m, 2H), 2.47 (s, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 2.01 (s, 3H). HRMS calcd. for M+H (C<sub>22</sub>H<sub>25</sub>N<sub>4</sub>): 345.2079. Found: 345.2061.

Examples 6-10 and 12-36 given in TABLE 1 may be prepared in the same manner as described for the preparation of Example 11, starting with the product from Example 11, Part E, and substituting the appropriate electrophile.

TABLE 1



Ex.	R¹	R²	R³	R⁴	R⁵	mp °C
1	CH₂cPr	Cl	Cl	Cl	H	190-192
2	CH(CH₂CH₃)₂	Cl	Cl	Cl	H	210-212
3	CH₂CH(CH₂CH₃)₂	Cl	Cl	Cl	H	112-114
4	benzyl	Cl	Cl	Cl	H	Amorphous
5	n-butyl	Cl	Cl	Cl	H	176-177
6	4-fluorobenzyl	Cl	Cl	Cl	H	
7	4-phenylbenzyl	Cl	Cl	Cl	H	
8	CH₂(2-tetrahydropyran)	Cl	Cl	Cl	H	
9	CH₂CH₂OCH₂CH₃	Cl	Cl	Cl	H	
10	CH₂CH(CH₂CH₃)₂	Me	Me	Me	H	Oil, MS
11	benzyl	Me	Me	Me	H	88-89
12	n-butyl	Me	Me	Me	H	122-123
13	CH₂(2-tetrahydropyran)	Me	Me	Me	H	
14	COPh	Me	Me	Me	H	
15	CH₂cPr	Cl	Cl	H	H	106-107
16	CH₂cPr	H	Cl	H	H	130-134
17	benzyl	Cl	Cl	Br	H	
18	benzyl	Br	Cl	Br	H	
19	benzyl	Cl	OMe	OMe	H	
20	benzyl	Br	OMe	OMe	H	
21	n-butyl	Et	Br	Et	H	
22	n-butyl	Et	Me	Et	H	
23	CH₂cPr	Me	OMe	H	H	
24	CH₂cPr	Me	Cl	H	H	
25	CH(CH₂CH₃)₂	Br	iPr	H	H	
26	CH(CH₂CH₃)₂	Br	Br	H	H	
27	CH(CH₂CH₃)₂	Cl	OMe	H	H	
28	CH(CH₂CH₃)₂	Cl	Me	Me	H	
29	benzyl	Cl	Me	Me	H	
30	CH₂CH₂OCH₂CH₃	Cl	Me	Me	H	
31	CH₂cPr	Cl	Cl	H	Cl	
32	CH(CH₂CH₃)₂	Me	Cl	H	Cl	
33	CH₂CH(CH₂CH₃)₂	Br	Me	H	Cl	
34	benzyl	Cl	Cl	H	F	
35	n-butyl	Cl	Me	H	F	
36	CH(CH₃)CH₂CH₂CH₃	Me	Me	H	F	

Example 38

**Preparation of 5-Ethyl-3-methyl-4-[1-(2-ethyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

5        Part A: The product from Example 1, Part A (15 g, 54.23 mmol) was suspended in propionic anhydride (40 ml) and allowed to stir at room temperature for 2 hours. The reaction was poured onto an ice slurry (500 ml) and stirred overnight. The resultant precipitate was  
10        filtered and dried to constant weight to afford 16.02 g (89%) of desired amido pyrazole.

Part B: The product from Part A (15.92 g, 47.86 mmol) was reduced with borane/THF complex (144 ml) in the same manner as described for the preparation of  
15        Example 1, Part C to afford an oil, 5.65 g (56%, based on recovered starting material). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.47 (s, 2H), 5.36 (s, 1H), 3.08 (bs, 1H), 3.05 (m, 2H), 2.26 (s, 3H), 1.57 (m, 2H), 0.92 (s, 3H, J=7.8 Hz).

20        Part C: The product from Step B (10.50 g, 32.97 mmol) was dissolved in ethanol (75 ml), cooled to 0°C, and treated with 1.0N HCl (0.5 ml) and isoamyl nitrite (4.41 ml, 32.97 mmol). The reaction was stirred 24 hours, cooled to 0°C and the resultant purple  
25        precipitate filtered and dried to constant weight to afford 8.64 g (75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.51 (s, 2H), 2.74 (m, 2H), 2.3 (s, 3H), 1.48 (m, 2H), 0.85 (t, 3H, J=7.2 Hz).

Part D: The product from Part C (8.47 g, 24.36  
30        mmol) was dissolved in pyridine (140 ml) and the homogeneous solution refluxed 14 hours. The reaction was concentrated *in-vacuo* to remove pyridine and purified via column chromatography on silica gel (800 g) eluting initially with ethyl acetate/hexanes (1/1) to

remove unreacted starting material, and then with ethyl acetate to afford desired imidazopyrazole, 2.87 g (36%), mp 221.0-223.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.82 (bs, 1H), 7.44 (s, 2H), 2.85 (q, 2H, J=7.8 Hz), 2.46 (s, 3H), 1.37 (t, 3H, J=7.5 Hz).

**Part E:** The product from Part D (0.10 g, 0.30 mmol) was reacted with sodium hydride (30 mg, 0.75 mmol) and 1-bromo-2-ethylbutane (170 µl, 1.20 mmol) in dimethylformamide (2.0 ml) as described for the preparation of Example 1, Part F. Title compound: mp 135.5-136.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 2H), 3.89 (d, 2H, J=7.2 Hz), 2.77 (q, 2H, J=7.5 Hz), 2.51 (s, 3H), 1.80 (m, 1H), 1.38 (m, 7H), 0.94 (t, 3H, 7.5 Hz).

15

**Example 40****Preparation of 4-Cyclopropylmethyl-5-ethyl-3-methyl-1-(2,4,6-trichloro) phenylimidazo[4,5-c]pyrazole**

The product from Example 38, Part D (0.02 g, 0.06 mmol) was reacted with sodium bis(trimethylsilyl)amide (152 µl, 0.09 mmol, 0.6M/toluene) and cyclopropylmethylbromide (11.8 µl, 0.12 mmol) in dimethylformamide (0.6 ml) in a 2.0 ml polypropylene well confined within a 96 well microtiter plate. The reaction was agitated for 1 hour at room temperature, heated for 30 minutes at 60°C, then treated with aminomethylpolystyrene (180 mg, 0.180 mmol, Advanced ChemTech, 1.00 mmol/g loading, Lot # 13312) for 1 hour. The reaction was filtered, dried to constant weight, and purified on a silica gel plug (0.70 g) eluting with a solvent gradient from hexanes/ethyl acetate (9/1) to hexanes/ethyl acetate (1/1) to afford title compound, 18.2 mg, mp 144.5-146.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44

(s, 2H), 3.94 (d, 2H, J=6.6 Hz), 2.79 (q, 2H, J=7.2 Hz), 2.52 (s, 3H), 1.59 (s, 6H), 1.35 (t, 3H, J=7.2 Hz), 1.26 (m, 1H), 0.66 (m, 2H), 0.40 (m, 2H). MS (CI) M+H=313.1.

5

Example 105

**Preparation of 5-Ethyl-3-methyl-4-[1-(1-n-propyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole:**

The product from Example 38, Part D (50 mg, 0.15 mmol) was reacted with sodium bis(trimethylsilyl)amide (630 µl, 0.38 mmol, 0.6M/toluene) and 4-bromoheptane (11.8 µl, 0.12 mmol) in dimethylformamide (1.5 ml). The reaction was heated to 60°C for 3 hours, then diluted with water (10 ml) and extracted with ethyl acetate (3 X 15 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated *in-vacuo* and the crude product purified by column chromatography on silica gel (20 g) eluting with hexanes/ethyl acetate (1/1) to afford the title compound as a crystalline solid, mp 113-114°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 2H), 4.10 (m, 1H), 2.83 (q, 2H, J=7.3 Hz), 2.54 (s, 3H), 1.84 (q, 4H, J=7.7 Hz), 1.34 (t, 3H, J=7.2 Hz), 1.20 (m, 4H), 0.91 (t, 3H, J=7.4 Hz). HRMS calcd. for M+ (C<sub>20</sub>H<sub>26</sub>N<sub>4</sub>Cl<sub>3</sub>): 426.1145. Found: 426.1130.

25

Example 106

**Preparation of 5-Ethyl-3-methyl-4-[1-(1-ethyl)pentane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

30 The product from Example 38, Part D (200 mg, 0.61 mmol) was reacted with sodium bis(trimethylsilyl)amide (2.50 ml, 1.52 mmol, 0.6M/toluene) and 3-bromoheptane (435 µg, 2.43 mmol) in dimethylformamide (6.0 ml) as



described for the preparation of Example 99. Title compound was obtained as a crystalline solid, mp 121-122°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 2H), 3.99 (m, 1H), 2.81 (q, 2H, J=7.3 Hz), 2.53 (s, 3H), 1.88 (m, 4H), 1.35 (t, 3H, J=7.3 Hz), 1.29 (m, 4H), 0.86 (t, 3H, J=6.9 Hz), 0.84 (t, 3H, J=6.7 Hz). HRMS calcd. for M+ H (C<sub>20</sub>H<sub>26</sub>N<sub>4</sub>Cl<sub>3</sub>): 427.1223. Found: 427.1213.

#### Example 107

10        **Preparation of 5-Ethyl-3-methyl-4-[1-(1-methyl)propane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole:**

The product from Example 38, Part D (200 mg, 0.61 mmol) was reacted with sodium bis(trimethylsilyl)amide (2.50 ml, 1.52 mmol, 0.6M/toluene) and 2-bromobutane (260 µl, 2.43 mmol) in dimethylformamide (6.0 ml) as described for the preparation of Example 105. Title compound was obtained as a crystalline solid, mp 113-114°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.45 (s, 2H), 4.2 (m, 1H), 2.83 (q, 2H, J=7.3 Hz), 2.56 (s, 3H), 1.91 (m, 2H), 1.57 (d, 3H, J=6.6 Hz), 1.33 (t, 3H, J=7.3 Hz), 0.86 (t, 3H, J=7.3 Hz). HRMS calcd. for M+H (C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>Cl<sub>3</sub>): 385.0754. Found: 385.0743.

25

#### Example 108

**Preparation of 5-Ethyl-3-methyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

          The product from Example 38, Part D (200 mg, 0.61 mmol) was reacted with sodium bis(trimethylsilyl)amide (2.50 ml, 1.52 mmol, 0.6M/toluene) and 2-bromopentane (300 µl, 2.43 mmol) in dimethylformamide (6.0 ml) as described for the preparation of Example 105. Title

compound was obtained as a viscous oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (s, 2H), 4.30 (m, 1H), 2.56 (s, 3H), 1.86 (m, 2H), 1.55 (d, 3H,  $J=6.9$  Hz), 1.33 (t, 3H,  $J=7.3$  Hz), 0.93 (t, 3H,  $J=7.3$  Hz). HRMS calcd. for  $\text{M}^+ \text{H}$  ( $\text{C}_{18}\text{H}_{22}\text{N}_4\text{Cl}_3$ ): 399.0910. Found: 399.0901.

#### Example 113

##### **Preparation of 5-Ethyl-4-methanesulfonylbenzyl-3-methyl-1-(2,4,6-trichloro) phenylimidazo[4,5-c]pyrazole:**

10

The product from Example 38, Part D (0.02 g, 0.06 mmol) was reacted with sodium bis(trimethylsilyl)amide (152  $\mu\text{l}$ , 0.09 mmol, 0.6M/toluene) and 4-methylsulfonylbenzyl chloride (121  $\mu\text{l}$ , 0.12 mmol as a 1.0 M solution in DMF) in dimethylformamide (0.6 ml) in a 2.0 ml polypropylene well as described for the preparation of Example 40. Title compound was obtained as a crystalline solid, mp 194.0-196.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d, 2H,  $J=8.1$  Hz), 7.46 (s, 2H), 7.32 (d, 2H,  $J=8.1$  Hz), 5.36 (s, 2H), 3.07 (s, 3H), 2.78 (q, 2H,  $J=7.7$  Hz), 2.19 (s, 3H), 1.32 (t, 3H,  $J=7.7$  Hz). HRMS calcd. for  $\text{M}+1$  ( $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_2\text{Cl}_3\text{S}_1$ ): 497.0373. Found: 497.0343.

25

#### Example 114

##### **Preparation of 4-Benzoyl-5-ethyl-3-methyl-1-(2,4,6-trichloro)phenylimidazo [4,5-c]pyrazole**

The product from Example 38, Part D (200 mg, 0.61 mmol) was dissolved with gentle heating in anhydrous methylene chloride (5 ml) and treated with 4-dimethylaminopyridine (15 mg, 0.12 mmol), diisopropylethylamine (160  $\mu\text{l}$ , 0.92 mmol) and benzoyl

chloride (78  $\mu$ l, 0.67 mmol). The reaction was stirred 1.5 hours at room temperature, concentrated directly in-vacuo and purified by column chromatography on silica gel (50 g) eluting with hexanes/ethyl acetate (2/1) to afford desired product, 189 mg (71%) as a crystalline solid, mp 169.0-170.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (d, 2H,  $J=8.0$  Hz), 7.75 (m, 1H), 7.59 (t, 2H,  $J=8.1$  Hz), 7.48 (s, 2H), 3.10 (q, 2H,  $J=7.3$  Hz), 1.54 (s, 3H), 1.38 (t, 3H,  $J=7.3$  Hz). HRMS calcd. for  $\text{M}^+$  ( $\text{C}_{20}\text{H}_{15}\text{N}_4\text{Cl}_3\text{O}_1$ ): 432.0311. Found: 432.0291. Anal. Calcd. for  $\text{C}_{20}\text{H}_{15}\text{N}_4\text{Cl}_3\text{O}_1$ : C, 55.39; H, 3.50; N, 12.92. Found: C, 55.65; H, 3.46; N, 12.52.

#### Example 115

#### Preparation of 4-Benzenesulfonyl-5-ethyl-3-methyl-1-(2,4,6-trichloro)phenyl imidazo[4,5-c]pyrazole

The product from Example 38, Part D (200 mg, 0.61 mmol) was dissolved with gentle heating in anhydrous methylene chloride (5 ml) and treated diisopropylethylamine (160  $\mu$ l, 0.92 mmol) and benzenesulfonyl chloride (86  $\mu$ l, 0.67 mmol). The reaction was stirred 20 hours at room temperature, concentrated directly in-vacuo and purified by column chromatography on silica gel (55 g) eluting with hexanes/ethyl acetate (2/1) to afford desired product, 150 mg (53%) as a crystalline solid, mp 189.0-190.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (d, 2H,  $J=8.8$  Hz), 7.72 (m, 1H), 7.58 (t, 2H,  $J=8.1$  Hz), 7.45 (s, 2H), 3.01 (q, 2H,  $J=7.3$  Hz), 2.65 (s, 3H), 1.30 (t, 3H,  $J=7.3$  Hz). HRMS calcd. for  $\text{M}+1$  ( $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{Cl}_3\text{S}_1$ ): 469.0060. Found: 469.0035. Anal. Calcd. for  $\text{C}_{19}\text{H}_{15}\text{N}_4\text{Cl}_3\text{O}_2\text{S}_1$ : C, 48.58; H, 3.23. Found: C, 48.93, H, 3.36.

Example 116**Preparation of 4-Diphenylmethyl-5-ethyl-3-methyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Example 38, Part D (330 mg, 1.0 mmol) was dissolved in anhydrous dimethylformamide (10 mL), and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 4.17 mL, 2.5 mmol) was added. The solution was heated to 60°C for one hour, then bromodiphenylmethane (988 mg, 4.0 mmol) was added and the reaction held at 100°C for 63 hours. The reaction was then cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to give the final product as a crystalline solid (183 mg, 37%), mp <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 2H), 7.39 (m, 6H), 7.14 (m, 4H), 6.69 (s, 1H), 2.85 (q, 2H, J=7.7 Hz), 1.38 (s, 3H), 1.29 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>26</sub>H<sub>22</sub>Cl<sub>3</sub>N<sub>4</sub>): 495.0910. Found: 495.0883.

Example 117**Preparation of 5-Ethyl-3-methyl-4-(1-phenylethyl)-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Example Banana, Part D (200 mg, 0.61 mmol) was dissolved in anhydrous dimethylformamide (6 mL), and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 2.50 mL, 1.52 mmol) was added. The solution was heated to 60°C for one hour, then (1-bromoethyl)benzene (451 mg, 2.44 mmol) was added. The reaction was held at 100°C for 24 hours. The reaction was then cooled to room

temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified  
5 by column chromatography (25% ethyl acetate/hexanes) to give the final product as a crystalline solid (135 mg, 31%), mp  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (s, 2H), 7.37 (m, 3H), 7.19 (m, 2H), 2.87 (dq, 2H,  $J=7.4$  Hz,  $J=1.1$  Hz), 1.98 (s, 3H), 1.96 (d, 3H,  $J=7.0$  Hz), 1.34 (t, 3H,  $J=7.5$   
10 Hz). HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{21}\text{H}_{20}\text{Cl}_3\text{N}_4$ ): 433.0753. Found: 433.0763. Anal. Calcd. for  $\text{C}_{21}\text{H}_{19}\text{Cl}_3\text{N}_4$ : C, 58.15; H, 4.42; N, 12.92. Found: C, 58.05; H, 4.38; N, 12.73.

#### Example 118

#### 15 Preparation of 4-Cyclopentyl-5-ethyl-3-methyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole

The compound prepared in Example Banana, Part D (330 mg, 1.0 mmol) was dissolved in anhydrous dimethylformamide (10 mL), and sodium  
20 bis(trimethylsilyl)amide (0.6 M in toluene, 4.17 mL, 2.5 mmol) was added. The solution was heated to 60°C for one hour, then bromocyclopentane (596 mg, 4.0 mmol) was added and the reaction held at 100°C for 63 hours. The reaction was then cooled to room temperature, and  
25 diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by preparative thin layer chromatography (25% ethyl acetate/hexanes) to give  
30 the final product as a crystalline solid (81 mg, 20%), mp  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (s, 2H), 4.58 (m, 1H), 2.84 (q, 2H,  $J=7.6$  Hz), 2.55 (s, 3H), 2.22 (m, 2H), 2.00 (m, 4H), 1.80 (m, 2H), 1.33 (t, 3H,  $J=7.7$  Hz). HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{18}\text{H}_{20}\text{Cl}_3\text{N}_4$ ): 397.0753. Found: 397.0755.

Anal. Calcd. for  $C_{18}H_{19}Cl_3N_4$ : C, 54.36; H, 4.82; N, 14.09.  
Found: C, 54.37; H, 4.84; N, 13.82.

Example 152

- 5       **Preparation of 4-(n-Butyl)-5-ethyl-3-ethyl-1-**  
          **(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**
- Step A: Sodium hydride (60% in mineral oil, 6.30  
          g, 157 mmol) was rinsed free of oil with cyclohexane,  
          fresh cyclohexane was added (200 mL), and this  
10       suspension was heated to reflux. A solution of ethyl  
          propionate (15.3 g, 150 mmol) and acetonitrile (6.77 g,  
          165 mmol) in cyclohexane (30 mL) was then added to the  
          sodium hydride suspension over 10 minutes, the reaction  
          was held at reflux for 16 hours, and cooled to room  
15       temperature. The reaction was extracted with water, and  
          the resulting aqueous solution acidified to pH 4 with  
          10% HCl. This solution was then extracted with ethyl  
          acetate, and the organic solution dried over anhydrous  
          magnesium sulfate and reduced *in vacuo* to leave the  
20       cyanoketone as an amber oil (5.60 g, 38%). This oil was  
          then dissolved in ethanol (500 mL), the reaction heated  
          to 40°C, and ammonium nitrate (2.3 g, 28.8 mmol) added.  
          Anhydrous ammonia was bubbled through the solution for  
          24 hours, then water (200 mL) was added and the ethanol  
25       removed *in vacuo*, then 0.3 N NaOH (200 mL) was added.  
          The aqueous solution was extracted with diethyl ether,  
          and the organic phase was dried over anhydrous magnesium  
          sulfate and reduced *in vacuo* to leave the  $\beta$ -  
          aminoacrylonitrile (2.82 g, 29.3 mmol, 51%). To this  
30       material was added 1N HCl (95 mL) and 2,4,6-  
          trichlorophenylhydrazine (4.13 g, 19.5 mmol), and this  
          mixture was refluxed for three hours. The reaction was  
          cooled to room temperature and the supernatant aqueous  
          phase was decanted and neutralized with 10% NaOH,  
35       producing an oil that solidifies upon stirring. The

- amorphous solid was recovered by filtration to give the product (5.16 g, 91%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (s, 2H), 5.52 (s, 1H), 3.49 (bs, 2H), 2.61 (q, 2H,  $J=7.7$  Hz), 1.25 (t, 3H,  $J=7.7$  Hz). HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{11}\text{H}_{11}\text{Cl}_3\text{N}_3$ ): 290.0018. Found: 289.9995. Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{Cl}_3\text{N}_3$ : C, 45.47; H, 3.48; N, 14.46. Found: C, 45.58; H, 3.34; N, 14.30.

- Step B: The compound prepared in Step A (5.16 g, 17.8 mmol) was suspended in propionic anhydride (11.4 mL, 88.8 mmol) at room temperature and allowed to stir for 2 hours, resulting in a homogeneous solution. Ice was added and the reaction stirred for 5 hours, causing a solid to form. The off-white solid was isolated by filtration to leave the product (5.52 g, 90%), mp 145-148°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (s, 2H), 6.70 (bs, 1H), 6.53 (bs, 1H), 2.70 (q, 2H,  $J=7.7$  Hz), 2.30 (q, 2H,  $J=7.3$  Hz), 1.29 (t, 3H,  $J=7.5$  Hz), 1.15 (t, 3H,  $J=7.3$  Hz). HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{14}\text{H}_{15}\text{Cl}_3\text{N}_3\text{O}$ ): 346.0281. Found: 346.0280. Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{Cl}_3\text{N}_3\text{O}$ : C, 48.51; H, 4.07; N, 12.12. Found: C, 48.51; H, 3.96; N, 12.07.

- Step C: The compound prepared in Step B (5.47 g, 15.8 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). To this suspension was added borane/THF complex (47.3 mL, 47.3 mmol), and the reaction was refluxed for 16 hours. The reaction was cooled to room temperature and excess borane was quenched with 10% NaOH (15 mL) until off-gassing ceased. The reaction was diluted with water and diethyl ether, the layers separated and the organic phase washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced in vacuo to leave a white solid, mp 138-140°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 (s, 2H), 5.43 (s,

1H), 3.41 (m, 1H), 3.12 (q, 2H, J=6.6 Hz), 2.80 (q, 2H, J=7.7 Hz), 1.58 (m, 2H), 1.29 (t, 3H, J=7.7 Hz), 0.92 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>17</sub>Cl<sub>3</sub>N<sub>3</sub>): 332.0488. Found: 332.0485.

5

Step D: The compound prepared in Step C was suspended in ethanol (30 mL), and 15 drops of 10% HCl were added. Upon addition of the HCl significant off-gassing occurred, and at the completion of the off-gassing the reaction mixture was homogeneous. Isoamyl nitrite (2.1 mL, 15.7 mmol) was then added, and the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, then reduced to dryness in vacuo to give a dark oil. This residue was purified by column chromatography (gradient elution of 25-50% ethyl acetate/hexanes) to give the final product as purple crystals (1.66 g, 29% from amide), mp 104-107°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.46 (bs, 1H), 7.50 (s, 2H), 3.17 (q, 2H, J=7.7 Hz), 2.75 (m, 2H), 1.49 (q, 2H, J=7.0 Hz), 1.46 (t, 3H, J=7.7 Hz), 0.85 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>16</sub>Cl<sub>3</sub>N<sub>4</sub>O): 361.0390. Found: 361.0386. Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>Cl<sub>3</sub>N<sub>4</sub>O: C, 46.50; H, 4.18; N, 15.49, Found: C, 46.78; H, 4.10; N, 15.50.

25

Step E: The compound prepared in Step D (1.56 g, 4.31 mmol) was dissolved in anhydrous pyridine (20 mL) and the solution heated to reflux for 16 hours. The solvent was removed in vacuo and the residue purified by column chromatography (50% ethyl acetate/hexanes) to afford the product as a brown solid. This solid was washed with ethyl ether to leave the product as a tan solid (517 mg, 35%), mp 242-243.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.60 (bs, 1H), 7.44 (s, 2H), 2.866 (q, 2H, J=7.6 Hz), 2.860 (q, 2H, J=7.5 Hz), 1.394 (t, 3H, J=7.7



Hz), 1.386 (t, 3H, J=7.7 Hz). HRMS Calcd. for M+H  
(C<sub>14</sub>H<sub>14</sub>Cl<sub>3</sub>N<sub>4</sub>): 343.0273. Found: 343.0284. Anal. Calcd.  
for C<sub>14</sub>H<sub>13</sub>Cl<sub>3</sub>N<sub>4</sub>: C, 48.93; H, 3.81; N, 16.30. Found: C,  
48.87; H, 3.61; N, 16.14.

5

Step F: The compound prepared in Step E (80 mg,  
0.23 mmol) was dissolved in anhydrous dimethylformamide  
(2.5 mL) and sodium bis(trimethylsilyl)amide (0.6 M in  
toluene, 0.97 mL, 0.58 mmol) was added. The solution  
10 was heated to 60°C for one hour, then 1-bromobutane (0.10  
mL, 0.92 mmol) was added. The reaction was held at 60°C  
for one hour, cooled to room temperature, and diluted  
with water and diethyl ether. The layers were separated  
and the organic phase washed with water, dried over  
15 anhydrous magnesium sulfate, and reduced to dryness in  
vacuo. The residue was purified by column  
chromatography (25% ethyl acetate/hexanes) to give the  
final product as a crystalline solid (53 mg, 58%), mp  
101-104°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 (s, 2H), 4.02  
20 (t, 2H, J=7.5 Hz), 2.87 (q, 2H, J=7.7 Hz), 2.79 (q, 2H,  
J=7.3 Hz), 1.84 (m, 2H), 1.39 (m, 8H), 1.01 (t, 3H,  
J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.18, 152.16,  
136.73, 136.14, 135.15, 133.77, 128.58, 120.94, 45.27,  
33.45, 21.31, 21.25, 20.04, 14.14, 13.74, 12.72. HRMS  
25 Calcd. for M+ (C<sub>18</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>4</sub>): 398.0829. Found: 398.0832.  
Anal. Calcd. for C<sub>18</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>4</sub>: C, 54.08; H, 5.30; N, 14.02.  
Found: C, 54.45; H, 5.22; N, 13.86.

#### Example 153

#### 30 Preparation of 4-(3,4-Difluorobenzyl)-5-ethyl-3- ethyl-1-(2,4,6-trichloro)phenylimidazo[4,5- c]pyrazole

The compound prepared in Step E, Example 152 (80  
mg, 0.23 mmol) was dissolved in anhydrous

dimethylformamide (2.5 mL) and sodium  
bis(trimethylsilyl)amide (0.6 M in toluene, 0.97 mL,  
0.58 mmol) was added. The solution was heated to 60°C  
for one hour, then  $\alpha$ -bromo-3,4-difluorotoluene (0.12 mL,  
5 0.92 mmol) was added. The reaction was held at 60°C for  
one hour, cooled to room temperature, and diluted with  
water and diethyl ether. The layers were separated and  
the organic phase washed with water, dried over  
anhydrous magnesium sulfate, and reduced to dryness in  
10 vacuo. The residue was purified by column  
chromatography (25% ethyl acetate/hexanes) to give the  
final product as a crystalline solid (74 mg, 68%), mp  
100-103°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 (s, 2H), 7.18  
(m, 1H), 6.87 (m, 2H), 5.24 (s, 2H), 2.76 (q, 2H, J=7.7  
15 Hz), 2.57 (q, 2H, J=7.6 Hz), 1.31 (t, 3H, J=7.6 Hz),  
1.17 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H  
(C<sub>21</sub>H<sub>18</sub>Cl<sub>3</sub>F<sub>2</sub>N<sub>4</sub>): 469.0550. Found: 469.0565. Anal. Calcd.  
for C<sub>21</sub>H<sub>17</sub>Cl<sub>3</sub>F<sub>2</sub>N<sub>4</sub> C, 53.69; H, 3.66; N, 11.93. Found: C,  
53.85; H, 3.52; N, 11.49.

20

#### Example 154

#### **Preparation of 4-[1-(1-Ethyl)butane]-5-ethyl-3-ethyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

25 The compound prepared in Step E, Example 152 (145  
mg, 0.42 mmol) was dissolved in anhydrous  
dimethylformamide (4 mL) and sodium  
bis(trimethylsilyl)amide (0.6 M in toluene, 1.76 mL,  
1.05 mmol) was added. The solution was heated to 60°C  
30 for one hour, then 3-bromohexane (277 mg, 1.68 mmol) was  
added. The reaction was held at 60°C for 24 hours, then  
held at 80°C for an additional 24 hours. The reaction

was then cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to give the final product as a crystalline solid (22 mg, 12%), mp 96.5-98.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 (s, 2H), 4.01 (m, 1H), 2.90 (q, 2H, J=7.3 Hz), 2.81 (q, 2H, J=7.7 Hz), 1.87 (m, 4H), 1.39 (t, 3H, J=7.5 Hz), 1.34 (t, 3H, J=7.5 Hz), 1.25 (m, 2H), 0.92 (t, 3H, J=7.3 Hz), 0.84 (t, 3H, J=7.5 Hz). HRMS Calcd. for M<sup>+</sup> (C<sub>20</sub>H<sub>25</sub>Cl<sub>3</sub>N<sub>4</sub>): 426.1130. Found: 426.1145.

15

Example 155

**Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-ethyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Step E, Example 152 (145 mg, 0.42 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.76 mL, 1.05 mmol) was added. The solution was heated to 60°C for one hour, then 2-bromopentane (0.21 mL, 1.68 mmol) was added. The reaction was held at 60°C for 24 hours, then held at 80°C for an additional 24 hours. The reaction was then cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to give the final product as a crystalline solid (20 mg, 11%), mp

87.5-89.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 (s, 2H), 4.29 (m, 1H), 2.93 (q, 2H, J=7.3 Hz), 2.82 (q, 2H, J=7.7 Hz), 1.87 (m, 2H), 1.55 (d, 3H, J=6.6 Hz), 1.40 (t, 3H, J=7.5 Hz), 1.33 (t, 3H, J=7.5 Hz), 1.20 (m, 2H), 0.93 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>24</sub>Cl<sub>3</sub>N<sub>4</sub>): 413.1066. Found: 413.1056.

#### Example 156

#### Preparation of 4-(n-Butyl)-5-ethyl-3-methoxymethyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole

Step A: A solution of methoxyacetonitrile (16.3 g, 0.23 mol) and acetonitrile (8.21 g, 0.20 mol) in tetrahydrofuran (50 mL) was added slowly at room temperature to potassium t-butoxide (1M in THF, 180 mL, 0.18 mol). A thick slurry resulted during the addition, and additional tetrahydrofuran (70 mL) was added. The reaction was heated to reflux for 24 hours, and was then slowly hydrolyzed with water (100 mL). This mixture was then extracted with dichloromethane, and the organic phase was dried over anhydrous magnesium sulfate, filtered and reduced *in vacuo* to leave a brown oil. This oil was then purified by vacuum distillation to give the β-aminoacrylonitrile as a light yellow solid (13.0 g, 116 mmol, 50%). To this solid was added 1N HCl (200 mL) and 2,4,6-trichlorophenylhydrazine (16.3 g, 77.0 mmol) and this mixture was heated at reflux for three hours. The reaction was cooled to room temperature and the supernatant aqueous phase was decanted and neutralized with 10% NaOH, producing an oil that solidifies upon stirring. The solid was isolated by filtration, then redissolved in 1N HCl and filtered to remove dark solids. The solution was neutralized to recover the product as a tan solid. The tarry residue from the reaction was dissolved in ethyl acetate and

extracted with 1N HCl, and this extract was neutralized with 10% NaOH to leave a brown oil which solidifies upon standing to give the product (combined with earlier product, 5.71 g, 24%), mp 103.5-106°C. <sup>1</sup>H NMR (300

5 MHz, CDCl<sub>3</sub>) δ 7.49 (s, 2H), 5.72 (s, 1H), 4.42 (s, 2H), 3.58 (bs, 2H), 3.38 (s, 3H). HRMS Calcd. for M+H (C<sub>11</sub>H<sub>11</sub>Cl<sub>3</sub>N<sub>3</sub>O): 305.9970. Found: 305.9974. Anal. Calcd. for C<sub>11</sub>H<sub>10</sub>Cl<sub>3</sub>N<sub>3</sub>O: C, 43.10; H, 3.30; N, 13.71. Found: C, 43.09; H, 3.23; N, 13.70.

10

Step B: The compound prepared in Step A (5.61 g, 18.3 mmol) was suspended in propionic anhydride (11.7 mL, 91.5 mmol) at room temperature and allowed to stir for 20 hours, resulting in a homogeneous solution. Ice  
15 was added and the reaction stirred for 5 hours, then diethyl ether was added and the phases were separated, the organic phase washed with saturated aqueous NaHCO<sub>3</sub>, then saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, then dried over anhydrous magnesium sulfate and reduced in vacuo to leave an oil.  
20 Ice was added to this oil and stirred for four hours, causing a solid to form. The solid was isolated by filtration to leave the product as an amorphous solid (5.42 g, 81%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 7.52 (s, 2H), 6.72 (m, 2H), 4.51 (s, 2H), 3.40 (s, 3H), 2.31 (m, 2H), 1.15  
25 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>15</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>2</sub>): 362.0230. Found: 362.0223. Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 46.37; H, 3.89; N, 11.59. Found: C, 46.51; H, 3.82; N, 11.55.

30

Step C: The compound prepared in Step B (5.32 g, 14.7 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). To this suspension was added borane/THF complex (47.3 mL, 47.3 mmol), and the reaction was refluxed for 16 hours. The reaction was cooled to room  
35 temperature and excess borane was quenched with 10% NaOH

(15 mL) until off-gassing ceased. The reaction was diluted with water and diethyl ether, the layers separated and the organic phase washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced in vacuo to leave an orange oil. This oil was purified by column chromatography (25% ethyl acetate/hexanes) to give a light yellow oil (3.75 g, 73%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (s, 2H), 5.59 (s, 1H), 4.44 (s, 2H), 3.40 (s, 3H), 3.10 (m, 3H), 1.58 (m, 2H), 0.92 (t, 3H,  $J=7.3$  Hz). Anal. Calcd. for  $\text{C}_{14}\text{H}_{18}\text{Cl}_3\text{N}_3\text{O}$ : C, 48.23; H, 4.64; N, 12.05. Found: C, 48.38; H, 4.50; N, 11.94. HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{14}\text{H}_{17}\text{Cl}_3\text{N}_3\text{O}$ ): 348.0437. Found: 348.0441.

Step D: The compound prepared in Step C was dissolved in ethanol (25 mL), and 15 drops of 10% HCl were added. Isoamyl nitrite (1.7 mL, 12.6 mmol) was then added, and the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, and then reduced to dryness in vacuo to give a dark oil. This residue was purified by column chromatography (gradient elution of 25-50% ethyl acetate/hexanes) to give the final product as a dark blue oil (1.05 g, 26%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.25 (bs, 1H), 7.55 (s, 2H), 5.04 (s, 2H), 3.56 (s, 3H), 2.76 (m, 2H), 1.49 (m, 2H), 0.86 (t, 3H,  $J=7.5$  Hz). HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{14}\text{H}_{16}\text{Cl}_3\text{N}_4\text{O}_2$ ): 377.0339. Found: 377.0318.

Step E: The compound prepared in Step D (1.05 g, 2.8 mmol) was dissolved in anhydrous pyridine (20 mL) and the solution heated to reflux for 16 hours. The solvent was removed in vacuo and the residue purified by column chromatography (50% ethyl acetate/hexanes) to afford the product as a brown solid. This solid was recrystallized from diethyl ether/ethyl acetate to give

the product as a light tan solid (505 mg, 50%), mp 165.5-167.0°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.89 (bs, 1H), 7.46 (s, 2H), 4.68 (s, 2H), 3.44 (s, 3H), 2.86 (q, 2H, J=7.7 Hz), 1.37 (t, 3H, J=7.7 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>14</sub>Cl<sub>3</sub>N<sub>4</sub>O): 359.0233. Found: 359.0242. Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>Cl<sub>3</sub>N<sub>4</sub>: C, 61.20; H, 5.50; N, 20.39; Cl, 12.90. Found: C, 61.18; H, 5.90; N, 20.34; Cl, 12.78.

Step F: The compound prepared in Step E (76 mg, 0.21 mmol) was dissolved in anhydrous dimethylformamide (3 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 0.88 mL, 0.53 mmol) was added. The solution was heated to 60°C for one hour, then 1-bromobutane (0.09 mL, 0.84 mmol) was added. The reaction was held at 60°C for 1.5 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to give the final product as an orange solid (46 mg, 53%), mp 65.5-67.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.45 (s, 2H), 4.67 (s, 2H), 4.08 (t, 2H, J=7.5 Hz), 3.41 (ws, 3H), 2.80 (q, 2H, J=7.7 Hz), 1.84 (m, 2H), 1.43 (m, 2H), 1.36 (t, 3H, J=7.7 Hz), 1.00 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>22</sub>Cl<sub>3</sub>N<sub>4</sub>O): 415.0870. Found: 415.0859.

#### Example 157

#### **Preparation of 4-(3,4-Difluorobenzyl)-5-ethyl-3-methoxymethyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Step E, Example 156 (76 mg, 0.21 mmol) was dissolved in anhydrous dimethylformamide (3 mL) and sodium

bis(trimethylsilyl)amide (0.6 M in toluene, 0.88 mL, 0.53 mmol) was added. The solution was heated to 60°C for one hour, then  $\alpha$ -bromo-3,4-difluorotoluene (0.11 mL, 0.84 mmol) was added. The reaction was held at 60°C for 5 1.5 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column 10 chromatography (10% ethyl acetate/hexanes) to give the final product as an orange solid (50 mg, 49%), mp 91.5-94.5°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (s, 2H), 7.16 (m, 1H), 6.90 (m, 2H), 5.30 (s, 2H), 4.45 (s, 2H), 3.30 (s, 3H), 2.77 (q, 2H,  $J=7.7$  Hz), 1.31 (t, 3H,  $J=7.7$  Hz).  $^{13}\text{C}$  15 NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.28, 152.56, 151.48, 148.87, 148.34, 148.17, 136.05, 135.76, 133.92, 133.23, 132.97, 128.68, 122.36, 122.30, 122.22, 121.83, 117.93, 117.70, 115.67, 115.43, 67.75, 57.75, 48.09, 21.45, 12.36. HRMS Calcd. for  $\text{M}+\text{H}$  ( $\text{C}_{21}\text{H}_{18}\text{Cl}_3\text{F}_2\text{N}_4\text{O}$ ): 485.0505. Found: 20 485.0514.

#### Example 158

#### **Preparation of 4-[1-(1-Ethyl)butane]-5-ethyl-3-methoxymethyl-1-(2,4,6-trichloro) 25 phenylimidazo[4,5-c]pyrazole**

The compound prepared in Step E, Example 156, (125 mg, 0.35 mmol) was dissolved in anhydrous dimethylformamide (4.0 mL) and sodium 30 bis(trimethylsilyl)amide (0.6 M in toluene, 1.45 mL, 0.87 mmol) was added. The solution was heated to 60°C for one hour, then 3-bromohexane (229 mg, 1.39 mmol) was added. The reaction was held at 60°C for 20 hours,



cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to give the final product as a white solid (27 mg, 17%), mp 117-119°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (s, 2H), 4.67 (d, 2H, J=1.4 Hz), 4.04 (m, 1H), 3.34 (s, 3H), 2.83 (q, 2H, J=7.3 Hz), 1.92 (m, 4H), 1.35 (t, 3H, J=7.5 Hz), 0.91 (t, 3H, J=7.3 Hz), 0.82 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 158.65, 153.50, 136.09, 135.62, 133.32, 131.87, 128.64, 67.93, 58.61, 56.77, 37.10, 28.38, 22.11, 19.88, 13.87, 12.84, 11.10. HRMS Calcd. for M+H (C<sub>20</sub>H<sub>26</sub>Cl<sub>3</sub>N<sub>4</sub>O): 443.1161. Found: 443.1172.

#### Example 159

##### Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methoxymethyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole

The compound prepared in Step E, Example 156 (125 mg, 0.35 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 0.97 mL, 0.58 mmol) was added. The solution was heated to 60°C for one hour, then 2-bromopentane (0.18 mL, 1.39 mmol) was added. The reaction was held at 60°C for 20 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to give the final product as a

crystalline solid (34 mg, 23%), mp 100.0-101.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (s, 2H), 4.69 (s, 2H), 4.32 (m, 1H), 3.36 (s, 3H), 2.84 (q, 2H, J=7.7 Hz), 2.05 (m, 1H), 1.85 (m, 1H), 1.58 (d, 3H, J=6.5 Hz), 1.34 (t, 3H, J=7.7 Hz), 1.18 (m, 2H), 0.92 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>24</sub>Cl<sub>3</sub>N<sub>4</sub>O): 429.1017. Found: 429.1016.

#### Example 161

10       **Preparation of 5-Ethyl-3-hydroxymethyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

This compound was obtained as the second eluting compound from the reaction described in Example 163 (see below) as a solid (1.51 g, 65%), mp 144-146°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (s, 2H), 4.90 (d, 2H, J=5.8 Hz), 4.33 (m, 1H), 3.27 (bs, 1H), 2.84 (q, 2H, J=7.5 Hz), 1.97 (m, 1H), 1.88 (m, 1H), 1.56 (d, 3H, J=6.9 Hz), 1.34 (t, 3H, J=7.7 Hz), 1.25 (m, 2H), 0.91 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+ (C<sub>17</sub>H<sub>19</sub>Cl<sub>3</sub>N<sub>4</sub>O): 415.0859. Found: 415.0860.

#### Example 163

25       **Preparation of 3-Bromomethyl-5-ethyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Example 159 (2.39 g, 5.56 mmol) was dissolved in dichloromethane and cooled to -78°C and BBr<sub>3</sub> (27.8 mL as 1.0 M in dichloromethane, 27.8 mmol) was added. The reaction was held at -78°C for one hour, then warmed to room temperature for 16 hours. The reaction was quenched with water (100 mL) and diluted with dichloromethane. The layers were separated and the organic phase washed with saturated sodium chloride,

dried over anhydrous magnesium sulfate, and reduced *in vacuo*. The residue was purified by column chromatography (gradient elution of 10-20% ethyl acetate/hexanes), the first eluting compound being the title product as an amorphous solid (660 mg, 25%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (s, 2H), 4.75 (s, 2H), 4.35 (m, 1H), 2.84 (q, 2H, J=7.5 Hz), 2.0 (m, 2H), 1.63 (d, 3H, J=8.4 Hz), 1.35 (t, 3H, J=7.5 Hz), 1.25 (m, 2H), 0.96 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>21</sub>Cl<sub>3</sub>BrN<sub>4</sub>): 477.0016. Found: 477.0020.

#### Example 164

##### Preparation of 4-Benzyl-5-isopropyl-3-methyl-1-(2,4,6-trichloro)phenyl-imidazo[4,5-c]pyrazole

**Part A:** The product from Example 1, Part A (9.96 g, 36.01 mmol) was suspended in isobutyric anhydride (25 ml), refluxed for 18 hours and allowed to stir at room temperature for 18 hours. The reaction was treated with water (200 ml) and 10% sodium hydroxide (100 ml) and stirred 2 hours. The reaction was then extracted with diethyl ether (3 X 100 ml), and the combined organic extracts dried over anhydrous magnesium sulfate, and concentrated *in-vacuo* and dried to constant weight to afford an amorphous solid, 12.48 g (100%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.51 (s, 2H), 6.71 (bs, 1H), 6.47 (bs, 1H), 2.39 (m, 1H), 2.33 (s, 3H), 1.24 (d, 3H, J=7.0 Hz), 1.13 (d, 3H, J=7.0 Hz).

**Part B:** The product from Part A (12.48 g, 36.00 mmol) was reduced with borane/THF complex (100 ml) in the same manner as described for the preparation of Example 1, Part C to afford an oil, 10.91 g (92%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.53 (s, 2H), 5.39 (s, 1H), 3.49 (m, 1H), 2.94 (t, 2H, J=4.5Hz), 2.39 (s, 3H).

Part C: The product from Step B (10.91 g, 32.80 mmol) was dissolved in ethanol (55 ml), cooled to 0°C, and treated with 1.0N HCl (0.5 ml) and isoamyl nitrite (4.40 ml, 32.80 mmol). The reaction was stirred for 3 hours while exposed to air, then concentrated to dryness *in-vacuo*, and purified by column chromatography on silica gel (800 g) eluting with hexanes/ethyl acetate (1/1) to afford a violet crystalline solid, 8.56 g (72%), mp 100-102°C. . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.53 (bs, 1H), 7.51 (s, 2H), 2.73 (s, 3H), 2.60 (t, 3H, J=6.3 Hz), 1.68 (m, 1H), 0.84 (d, 6H, J=7.2 Hz).

Part D: The product from Part C (8.56 g, 23.67 mmol) was dissolved in pyridine (143 ml) and the homogeneous solution refluxed 20 hours. The reaction was concentrated *in-vacuo* to remove pyridine and purified via column chromatography on silica gel (800 g) eluting initially with ethyl acetate/hexanes (1/1) and then hexanes/ethyl acetate (1/2) to afford desired imidazopyrazole, 1.49 g (18%), mp 139-139.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.81 (bs, 1H), 7.44 (s, 2H), 3.13 (m, 1H), 2.46 (s, 3H), 1.39 (d, 6H, J=7.0 Hz).

Part E: The product from Part D (0.10 g, 0.29 mmol) was reacted with sodium hydride (30 mg, 0.75 mmol) and benzyl bromide (138 μl, 1.16 mmol) in dimethylformamide (2.0 ml) as described for the preparation of Example 1, Part F. Title compound: mp 103-105°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 2H), 7.35 (m, 3H), 7.11 (d, 2H, J=6.6Hz), 5.29 (s, 2H), 3.07 (m, 1H), 2.15 (s, 3H), 1.32 (d, 6H, J=7.0 Hz). HRMS calcd. for M<sup>+</sup> (C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>Cl<sub>3</sub>): 432.0675. Found: 432.0660. Anal. Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>Cl<sub>3</sub>: C, 58.14; H, 4.42; N, 12.92. Found: C, 58.30; H, 4.29; N, 12.70.

Example 165**Preparation of 4-(n-Butyl)-5-isopropyl-3-methyl-1-(2,4,6-trichloro)phenyl imidazo[4,5-c]pyrazole**

The product from Example 164, Step D (100 mg, 0.29 mmol) was reacted with sodium hydride (30 mg, 0.75 mmol) and n-butyl bromide (125  $\mu$ l, 1.16 mmol) in dimethylformamide (2.0 ml) as described for the preparation of Example 1, Part F. Title compound: mp 85.0-86.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (s, 2H), 4.03 (t, 2H, J=7.3 Hz), 3.05 (m, 1H), 2.51 (s, 3H), 1.84 (m, 2H), 1.45 (m, 2H), 1.36 (d, 6H, J=7.6 Hz), 1.01 (t, 3H, J=7.3 Hz). HRMS calcd. for  $\text{M}^+$  ( $\text{C}_{18}\text{H}_{21}\text{N}_4\text{Cl}_3$ ): 398.0832. Found: 398.0819.

15

Example 166**Preparation of 5-Isopropyl-3-methyl-4-[1-(3-methyl)butane]-1-(2,4,6-trichloro)phenyl imidazo[4,5-c]pyrazole**

The product from Example 164, Step D (100 mg, 0.29 mmol) was reacted with sodium hydride (30 mg, 0.75 mmol) and 1-bromo-2-ethylbutane (160  $\mu$ l, 1.16 mmol) in dimethylformamide (2.0 ml) as described for the preparation of Example 1, Part F. Title compound: mp 88.0-91.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (s, 2H), 3.92 (d, 2H, J=6.6 Hz), 3.03 (m, 1H), 2.50 (s, 3H), 2.78 (m, 1H), 1.35 (d, 6H, J=7.0 Hz), 1.40-1.25 (m, 4H), 0.94 (t, 6H, J=7.3 Hz). HRMS calcd. for  $\text{M}^+$  ( $\text{C}_{20}\text{H}_{25}\text{N}_4\text{Cl}_3$ ): 426.1145. Found: 412.1143.

30

Example 167

**Preparation of 5-Isopropyl-3-methyl-4-[1-(3-methyl)butane]-1-(2,4,6-trichloro)phenyl  
imidazo[4,5-c]pyrazole**

5        The product from Example 164, Step D (100 mg, 0.29 mmol) was reacted with sodium hydride (30 mg, 0.75 mmol) and 1-bromo-3-methylbutane (140  $\mu$ l, 1.16 mmol) in dimethylformamide (2.0 ml) as described for the preparation of Example 1, Part F. Title compound: mp  
10    87.0-89.0°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (s, 2H), 4.04 (m, 2H), 3.02 (m, 1H), 2.52 (s, 3H), 1.76 (m, 3H), 1.36 (d, 6H,  $J=7.0$  Hz), 1.23 (m, 2H), 1.03 (d, 6H,  $J=6.2$  Hz). HRMS calcd. for  $\text{M}^+$  ( $\text{C}_{19}\text{H}_{23}\text{N}_4\text{Cl}_3$ ): 412.0988. Found: 412.0988. Anal. Calcd. for  $\text{C}_{19}\text{H}_{23}\text{N}_4\text{Cl}_3$ : C, 55.15; H, 5.60; N, 13.54. Found: C, 55.44; H, 5.50; N, 13.17.

Example 238

20        **Preparation of 5-Ethyl-3-formyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

      Dess-Martin periodinane (1.84 g, 4.33 mmol) was dissolved in anhydrous acetonitrile (3 mL), and to this was added the compound prepared in Example 161 (1.50 g, 3.61 mmol) suspended in anhydrous acetonitrile (60 mL).  
25    The reaction was stirred at room temperature for 30 minutes, and was then diluted with diethyl ether. The reaction was quenched with 0.5 N NaOH and the phases were separated, the organic phase was washed with  
30    saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to give the product as an amorphous white solid (1.43 g, 96%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.97

(s, 1H), 7.52 (s, 2H), 4.43 (m, 1H), 2.88 (q, 2H, J=7.5 Hz), 2.16 (m, 1H), 1.95 (m, 1H), 1.66 (d, 3H, J=7.0 Hz), 1.36 (t, 3H, J=7.5 Hz), 1.27 (m, 1H), 1.11 (m, 1H), 0.89 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>20</sub>Cl<sub>3</sub>N<sub>4</sub>O): 413.0703. Found: 413.0704.

#### Example 243

##### Preparation of 5-Ethyl-3-(1-hydroxyethyl)-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)

##### 10 phenylimidazo[4,5-c]pyrazole

The compound prepared in Example 238 (1.38 g, 3.33 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL) and cooled to -78°C. To this solution was added methylmagnesium bromide (2.11 mL, 3.0 M in diethyl  
15 ether, 6.33 mmol) and the reaction was held at -78°C for one hour, then the temperature was gradually increased to room temperature. After three hours at room temperature, the reaction was quenched with 15% aqueous ammonium chloride and diethyl ether was added. The  
20 organic phase was dried over anhydrous magnesium sulfate and reduced in vacuo. The residue was purified by chromatography (20% ethyl acetate/hexanes) to give the desired mixture of diastereomers as a white solid (950 mg, 66%), mp 182.0-184.0 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ  
25 7.45 (s, 2H), 5.15 (m, 1H), 4.40 (m, 1H), 2.83 (q, 2H, J=7.5 Hz), 2.28 (d, 0.5H, J=7.7 Hz), 2.23 (d, 0.5H, J=7.7 Hz), 2.0 (m, 2H), 1.72 (d, 1.5H, J=6.6 Hz), 1.72 (d, 1.5H, J=6.6 Hz), 1.56 (m, 3H), 1.34 (t, 3H, J=7.7 Hz), 0.93 (t, 1.5H, J=7.3 Hz), 0.921 (t, 1.5H, J=7.3  
30 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>24</sub>Cl<sub>3</sub>N<sub>4</sub>O): 429.1016. Found: 429.1010. Anal. Calcd. for (C<sub>19</sub>H<sub>23</sub>Cl<sub>3</sub>N<sub>4</sub>O): C, 53.10; H, 5.39; N, 13.04. Found: C, 53.11; H, 5.41; N, 12.64.

Example 251**Preparation of 3-Acetyl-5-ethyl-4-[1-(1-methyl)butane]-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole**

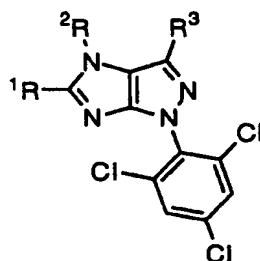
- 5 Dess-Martin periodinane (1.12 g, 2.65 mmol) was suspended in anhydrous dichloromethane (5 mL) and to this solution was added the compound prepared in Example 243 (950 mg, 2.21 mmol) in anhydrous dichloromethane (100 mL). The reaction was held at room temperature for
- 10 two hours, and was then quenched with 0.5 N NaOH (200 mL). Diethyl ether was added and the organic phase was dried over anhydrous magnesium sulfate and reduced *in vacuo*. The residue was purified by chromatography (gradient elutions with 10-20% ethyl acetate/hexanes) to
- 15 give the final product as a white solid (768 mg, 81%), mp 50.0-52.0°C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 120°C) δ 7.88 (s, 2H), 4.66 (m, 1H), 2.85 (q, 1H, J=7.5 Hz), 2.84 (q, 1H, J=7.4 Hz), 2.05 (m, 1H), 1.90 (m, 1H), 1.57 (d, 3H, J=6.8 Hz), 1.28 (m, 4H, includes 1.26 (t, 3H, J=7.5 Hz),
- 20 1.09 (m, 1H), 0.83 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>22</sub>Cl<sub>3</sub>N<sub>4</sub>O): 427.0859. Found: 427.0853. Anal. Calcd. for C<sub>19</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>4</sub>O: C, 53.35; H, 4.96; N, 13.10. Found: C, 53.55; H, 4.91; N, 13.11.

- 25 The Examples in Table 2 may be prepared as exemplified above for the preparation of Examples 38, 40, 105-108, 113-118, 152-159, 161, 163-167, 238, 243, and 251.

30



TABLE 2



Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp °C
37	Et	CH <sub>2</sub> Ph	Me	129-131
38	Et	CH <sub>2</sub> CH(Et) <sub>2</sub>	Me	135-136
39	Et	CH <sub>2</sub> CH <sub>2</sub> CH(Me) <sub>2</sub>	Me	109-110
40	Et	CH <sub>2</sub> cPr	Me	144-146
41	Et	n-butyl	Me	115-117
42	Et	n-propyl	Me	110-113
43	Et	CH(Et) <sub>2</sub>	Me	110-111
44	Et	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CN	Me	Oil, MS
45	Et	CH <sub>2</sub> CH <sub>2</sub> CN	Me	192-194
46	Et	4-methoxybenzyl	Me	134-136
47	Et	3-methoxybenzyl	Me	Oil, MS
48	Et	2-methylbenzyl	Me	135-137
49	Et	3-methylbenzyl	Me	155-156
50	Et	4-methylbenzyl	Me	133-134
51	Et	2,4-dimethylbenzyl	Me	Oil, MS
52	Et	2,5-dimethylbenzyl	Me	130-133
53	Et	3,4-dimethylbenzyl	Me	125-127
54	Et	3,5-dimethylbenzyl	Me	157-157
55	Et	4-tertbutylbenzyl	Me	104-105
56	Et	2-phenylbenzyl	Me	126-127
57	Et	4-phenylbenzyl	Me	140-141
58	Et	2-bromobenzyl	Me	151-153
59	Et	3-bromobenzyl	Me	147-148
60	Et	4-bromobenzyl	Me	192-194
61	Et	2-chlorobenzyl	Me	158-159
62	Et	3-chlorobenzyl	Me	140-141
63	Et	4-chlorobenzyl	Me	193-195
64	Et	2,4-dichlorobenzyl	Me	194-195
65	Et	2,6-dichlorobenzyl	Me	130-132
66	Et	3,4-dichlorobenzyl	Me	187-188
67	Et	2-chloro-6-fluorobenzyl	Me	146-147
68	Et	2-fluorobenzyl	Me	127-129
69	Et	3-fluorobenzyl	Me	136-137
70	Et	4-fluorobenzyl	Me	130-132
71	Et	2,4-difluorobenzyl	Me	151-152

TABLE 2 (Continued)

Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp °C
72	Et	2,5-difluorobenzyl	Me	162-163
73	Et	3,4-difluorobenzyl	Me	154-155
74	Et	3,5-difluorobenzyl	Me	139-140
75	Et	2-trifluoromethylbenzyl	Me	177-178
76	Et	3-trifluoromethylbenzyl	Me	176-178
77	Et	4-trifluoromethylbenzyl	Me	167-168
78	Et	2,4-bis(trifluoromethyl)benzyl	Me	150-151
79	Et	3,5-bis(trifluoromethyl)benzyl	Me	144-145
80	Et	3,5-dimethoxybenzyl	Me	139-140
81	Et	4-methoxy-3-methylbenzyl	Me	149-150
82	Et	4-benzyloxybenzyl	Me	115-117
83	Et	2-cyanobenzyl	Me	220-221
84	Et	3-cyanobenzyl	Me	149-152
85	Et	4-cyanobenzyl	Me	205-206
86	Et	3-trifluoromethoxybenzyl	Me	93-96
87	Et	4-trifluoromethoxybenzyl	Me	79-81
88	Et	2-nitrobenzyl	Me	>250
89	Et	3-nitrobenzyl	Me	>250
90	Et	4-nitrobenzyl	Me	>250
91	Et	2-methyl-3-nitrobenzyl	Me	>250
92	Et	4-acetamidobenzyl	Me	Oil, MS
93	Et	CH <sub>2</sub> CH <sub>2</sub> CH(OiPr) 4-methylphenyl	Me	Oil, MS
94	Et	CH <sub>2</sub> CH <sub>2</sub> CH(OMe) 4-chlorophenyl	Me	Oil, MS
95	Et	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CF <sub>3</sub>	Me	138-140
96	Et	geranyl	Me	151-152
97	Et	CH <sub>2</sub> CH=CHPh	Me	Oil, MS
98	Et	CH <sub>2</sub> (cyclohexyl)	Me	149-150
99	Et	CH <sub>2</sub> CH(Me) <sub>2</sub>	Me	131-132
100	Et	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CCH	Me	145-146
101	Et	nPentyl	Me	142-143
102	Et	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	Me	195-196
103	Et	CH <sub>2</sub> (2-tetrahydropyran)	Me	Oil, MS
104	Et	CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	Me	118-120
105	Et	CH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	113-114
106	Et	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	121-122
107	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	Me	113-114
108	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	93-95
109	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	Oil, MS
110	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	119-120
111	Et	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	Oil, MS
112	Et	4-methylcyclohexyl	Me	Oil, MS

TABLE 2 (Continued)

Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp °C
113	Et	4-methanesulfonylbenzyl	Me	194-196
114	Et	COPh	Me	169-170
115	Et	SO <sub>2</sub> Ph	Me	189-190
116	Et	CH(phenyl) <sub>2</sub>	Me	170-172
117	Et	CH(CH <sub>3</sub> )phenyl	Me	166-168
118	Et	cyclopentyl	Me	125-128
119	Et	cyclohexyl	Me	
120	Et	CH <sub>2</sub> (2-tetrahydrofuran)	Me	
121	Et	CH <sub>2</sub> CH <sub>2</sub> COPh	Me	
122	Et	CH <sub>2</sub> CH <sub>2</sub> CO(4-fluorophenyl)	Me	
123	Et	CH <sub>2</sub> CH <sub>2</sub> COCH <sub>2</sub> CH <sub>3</sub>	Me	
124	Et	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COCH <sub>3</sub>	Me	
125	Et	CH <sub>2</sub> CH <sub>2</sub> NHCOPh	Me	
126	Et	2,4,6-trimethylbenzyl	Me	
127	Et	2-picolyl	Me	
128	Et	3-picolyl	Me	
129	Et	4-picolyl	Me	
130	Et	2-methylquinoline	Me	
131	Et	n-butyl	H	80-82
132	Et	benzyl	H	86-89
133	Et	3,4-difluorobenzyl	H	145-147
134	Et	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	H	Oil, MS
135	Et	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	Oil, MS
136	Et	CH <sub>2</sub> -2-tetrahydropyranyl	H	Oil, MS
137	Et	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	Oil, MS
138	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	90-92
139	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	Oil, MS
140	n-Pr	n-butyl	H	Oil, MS
141	n-Pr	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	Oil, MS
142	n-Pr	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	Oil, MS
143	n-Pr	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	Oil, MS
144	n-Pr	n-butyl	Me	94-95
145	n-Pr	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	91-93
146	n-Pr	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	113-115
147	n-Pr	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	98-100
148	c-Pr	n-butyl	Me	91-93
149	c-Pr	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	120-122
150	c-Pr	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	152-155
151	c-Pr	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	102-105
152	Et	n-butyl	Et	101-104
153	Et	3,4-difluorobenzyl	Et	Oil, MS

TABLE 2 (Continued)

Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp °C
154	Et	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Et	96-98
155	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Et	88-90
156	Et	n-butyl	CH <sub>2</sub> OCH <sub>3</sub>	66-68
157	Et	3,4-difluorobenzyl	CH <sub>2</sub> OCH <sub>3</sub>	Oil, MS
158	Et	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	117-119
159	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	100-102
160	Et	n-butyl	CH <sub>2</sub> OH	163-165
161	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> OH	144-146
162	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> F	Oil, MS
163	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> Br	Oil, MS
164	i-Pr	benzyl	Me	103-105
165	i-Pr	n-butyl	Me	85-86
166	i-Pr	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	88-91
167	i-Pr	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	87-89
168	i-Pr	n-butyl	H	
169	i-Pr	benzyl	H	
170	i-Pr	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	H	
171	i-Pr	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	
172	n-Bu	n-butyl	Me	
173	n-Bu	benzyl	Me	
174	n-Bu	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	
175	n-Bu	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	
176	Ph	n-butyl	Me	
177	Ph	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
178	Ph	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	
179	Ph	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
180	Ph	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	
181	Ph	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
182	CF <sub>3</sub>	n-butyl	Me	
183	CF <sub>3</sub>	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
184	CF <sub>3</sub>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	
185	CF <sub>3</sub>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
186	CF <sub>3</sub>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Et	
187	CF <sub>3</sub>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Et	
188	Et	n-butyl	CF <sub>3</sub>	
189	Et	CH(CH <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub>	
190	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CF <sub>3</sub>	
191	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub>	
192	Et	n-butyl	CHF <sub>2</sub>	
193	Et	benzyl	CHF <sub>2</sub>	
194	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CHF <sub>2</sub>	

TABLE 2 (Continued)

Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp °C
195	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>	
196	Et	CH <sub>2</sub> CH <sub>2</sub> SCH <sub>2</sub> CH <sub>3</sub>	Me	
197	Et	CH <sub>2</sub> CH <sub>2</sub> OPh	Me	
198	Et	CH <sub>2</sub> CH(CH <sub>3</sub> )CN	Me	
199	Et	(CH <sub>2</sub> ) <sub>4</sub> CN	Me	
200	Et	2-methoxybenzyl	Me	
201	Et	2-methoxy-5-nitrobenzyl	Me	
202	Et	2-hydroxy-5-nitrobenzyl	Me	
203	Et	CH <sub>2</sub> CH <sub>2</sub> Ph	Me	
204	Et	(CH <sub>2</sub> ) <sub>3</sub> Ph	Me	
205	Et	CH <sub>2</sub> CH <sub>2</sub> N(i-Pr) <sub>2</sub>	Me	
206	Et	CH <sub>2</sub> CH <sub>2</sub> -morpholino	Me	
207	Et	5-methyl-2-nitrobenzyl	Me	
208	Et	2-pentanone	Me	
209	Et	2,4,6-trifluorobenzyl	Me	
210	Et	CH(COphenyl)CH <sub>3</sub>	Me	
211	Et	CH(COphenyl)CH(CH <sub>3</sub> ) <sub>2</sub>	Me	
212	Et	CH(COphenyl)phenyl	Me	
213	Et	CH(COphenyl)benzyl	Me	
214	Et	CH(CO <sub>2</sub> CH <sub>3</sub> )phenyl	Me	
215	Et	CH(CO <sub>2</sub> CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
216	Et	CH(COCH <sub>3</sub> )CH <sub>3</sub>	Me	
217	Et	CH <sub>2</sub> CH(OH)CH <sub>2</sub> Ophenyl	Me	
218	Et	CH <sub>2</sub> CH(OH)phenyl	Me	
219	Et	CH <sub>2</sub> CH(OH)benzyl	Me	
220	Et	CH <sub>2</sub> CH(OH)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
221	Et	CH <sub>2</sub> COCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
222	Et	CH <sub>2</sub> CObenzyl	Me	
223	Et	CH <sub>2</sub> CH(OMe)benzyl	Me	
224	Et	CO(4-chlorophenyl)	Me	
225	Et	CO(2-methoxyphenyl)	Me	
226	Et	COCH(CH <sub>2</sub> CH <sub>3</sub> )phenyl	Me	
227	Et	CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
228	Et	CO <sub>2</sub> phenyl	Me	
229	Et	CON(CH <sub>3</sub> )phenyl	Me	
230	Et	COmorpholino	Me	
231	Et	SO <sub>2</sub> (2-thiophene)	Me	
232	Et	SO <sub>2</sub> benzyl	Me	
233	Et	SO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	
234	Et	CON(CH <sub>3</sub> )phenyl	H	
235	Et	COmorpholino	CF <sub>3</sub>	

TABLE 2 (Continued)

Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp °C
236	Et	SO <sub>2</sub> (2-thiophene)	CF <sub>3</sub>	
237	Et	n-butyl	CHO	
238	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CHO	Oil, MS
239	Et	benzyl	CHO	
240	Et	CH <sub>2</sub> cPr	CH(CH <sub>3</sub> )OH	
241	Et	n-butyl	CH(CH <sub>3</sub> )OH	
242	Et	benzyl	CH(CH <sub>3</sub> )OH	
243	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH(CH <sub>3</sub> )OH	182-184
244	Me	benzyl	CH(Ph)OH	
245	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH(Ph)OH	
246	Et	n-butyl	CO <sub>2</sub> H	
247	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> H	
248	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> Et	
249	Et	n-butyl	CO <sub>2</sub> Et	
250	Et	benzyl	COMe	
251	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	COMe	50-52
252	Et	n-butyl	COMe	
253	Et	3,4-difluorobenzyl	COMe	
254	Et	4-fluorobenzyl	COMe	
255	Et	cyclopentyl	COMe	
256	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> NH <sub>2</sub>	
257	Et	benzyl	CH <sub>2</sub> NH <sub>2</sub>	
258	Et	CH <sub>2</sub> cPr	CH <sub>2</sub> NHMe	
259	Et	n-butyl	CH <sub>2</sub> NHMe	
260	Et	benzyl	CH <sub>2</sub> NMe <sub>2</sub>	
261	Et	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> NMe <sub>2</sub>	

Example 263

5      **Preparation of 4-Benzyl-5-ethyl-3-methyl-1-(2,4,6-trimethyl)phenyl-imidazo[4,5-c]pyrazole**

10      **Step A:** The product from Example 11, Part A (10 g, 46.44 mmol) was suspended in propionic anhydride (30 ml) and allowed to stir at room temperature for 2 hours. The reaction was poured onto an ice slurry (500 ml) and stirred overnight. The resultant precipitate was filtered and dried to constant weight to afford 11.92 g (95%) of desired amido pyrazole, mp 171.5-173°C. <sup>1</sup>H

NMR (300 MHz, CDCl<sub>3</sub>) δ 6.98 (s, 2H), 6.74 (bs, 1H), 6.54 (s, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 2.24 (q, 2H, J=7.3 Hz), 1.96 (s, 3H), 1.13 (t, 3H, J=7.3 Hz).

Step B: The product from Step A (11.5 g, 42.37 mmol) was reduced with lithium aluminum hydride (84.75 ml, 84.74 mmol, 1.0 M/THF) as described for the preparation of Example 11, Step C. The product was obtained as a clear viscous oil, 10.81 g (99%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.93 (s, 2H), 5.31 (s, 1H), 3.02 (m, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 1.99 (s, 6H), 1.53 (m, 2H), 0.88 (t, 3H, J=7.3 Hz).

Step C: The product from Step B (10.81 g, 41.99 mmol) was treated with isoamyl nitrite (5.62 ml, 41.99 mmol) as described for the preparation of Example 11, Step D to afford a purple crystalline solid, 9.59 g (80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.07 (bs, 1H), 6.94 (s, 2H), 2.70 (s, 3H), 2.62 (q, 2H, J=6.8 Hz), 2.36 (s, 3H), 2.09 (s, 6H), 1.36 (m, 2H), 0.77 (t, 3H, J=7.3 Hz).

Step D: The product from Step C (9.59 g) was refluxed in pyridine (60 ml) for 16 hours, as described for the preparation of Example 11, Step E. Chromatography on silica gel (700 g) eluting with hexanes/ethyl acetate (1/1) yielded recovery of 2.38 g of starting material, while elution with ethyl acetate alone afforded the desired product, 3.41 g (50% based on recovered starting material). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.67 (bs, 1H), 6.86 (s, 2H), 2.71 (q, 2H, J=7.8 Hz), 2.38 (s, 3H), 2.27 (s, 3H), 1.99 (s, 6H), 1.28 (t, 3H, J=7.8 Hz).

Step E: The product from Step D (0.25 g, 0.93 mmol) was treated with sodium hydride (93 mg, 2.32 mmol) and benzyl bromide (443 μl, 3.7 mmol) in anhydrous dimethylformamide (15 ml) as described for the

preparation of Example 11, Step F. Title compound:

200.0 mg (60%), mp 96.5-98°C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ  
7.35 (m, 3H), 7.14 (d, 2H, J=6.6 Hz), 6.90 (s, 2H), 5.26  
(s, 2H), 2.77 (q, 2H, J=7.7 Hz), 2.29 (s, 3H), 2.16 (s,  
5 3H), 2.02 (s, 6H), 1.29 (t, 3H, J=7.7 Hz).

#### Example 325

#### Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-chloro-4-bromo)phenylimidazo[4,5-c]pyrazole

10     Step A: β-Aminocrotononitrile (8.62 g, 0.10 mol)  
was dissolved in 1.0N HCl (275 ml) and treated with 2-chloro-4-bromophenylhydrazine (0.1 mol). The reaction  
was refluxed 4h, cooled, and decanted into a 2 liter  
beaker. The solution was diluted with water (250 ml)  
15 and neutralized with 10% NaOH (125 ml). The resultant  
precipitate was filtered and dried to constant weight to  
afford 22.71 g (79%) of the desired aminopyrazole as a  
white crystalline solid, mp 125.0-126.0°C. <sup>1</sup>H NMR (300  
MHz, CDCl<sub>3</sub>) δ 7.69 (d, 1H, J=2.0 Hz), 7.51 (dd, 1H,  
20 J=2.0, 7.0 Hz), 7.34 (d, 1H, J=7.0 Hz), 5.46 (s, 1H),  
3.58 (bs, 2H), 2.23 (s, 3H).

Step B: The compound prepared in Step A (4.0g,  
14.0 mmol) was suspended in propionic anhydride (9.0 mL,  
25 69.8 mmol) at room temperature and was allowed to stir  
for 16 hours. Ice was then added and the reaction  
stirred for 5 hours. Diethyl ether was added and the  
phases were separated. The organic phase was washed  
with saturated sodium chloride, dried over anhydrous  
30 magnesium sulfate and reduced *in vacuo* to leave a thick  
oil. This residue was purified by column chromatography  
(50% ethyl acetate/hexanes) to give the final product as  
a solid (4.2 g, 88%), mp 107-110°C. <sup>1</sup>H NMR (300



5 MHz, CDCl<sub>3</sub>) δ 7.71 (d, 1H, J=2.2 Hz), 7.54 (dd, 1H, J=8.4 Hz, J=2.2 Hz), 7.35 (d, 1H, J=8.4 Hz), 6.91 (bs, 1H), 6.44 (s, 1H), 2.31 (s, 3H), 2.28 (m, 2H), 1.14 (m, 3H).  
13C NMR (75 MHz, CDCl<sub>3</sub>) δ 150.61, 137.18, 134.68, 133.02, 132.62, 131.39, 123.73, 99.01, 29.82, 14.04, 9.30.  
Anal. Calcd. for C<sub>13</sub>H<sub>13</sub>BrClN<sub>3</sub>O: C, 45.57; H, 3.82; N, 12.26. Found: C, 45.76; H, 3.83; N, 12.26.

10        Step C: The compound prepared in Step B (4.1 g, 12.0 mmol) was suspended in tetrahydrofuran (30 mL). To this suspension was added borane/THF complex (36.0 mL, 36.0 mmol), and the reaction refluxed for 3 hours. The reaction was cooled to room temperature and excess borane was quenched with 10% NaOH (10 mL) until off-gassing ceased and the reaction was diluted with water and diethyl ether. The layers were separated and the organic phase was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced in vacuo. This residue was purified by column chromatography (25% ethyl acetate/hexanes) to provide the final product as a white solid (3.46 g, 88%), mp 140-141.5°C. 1H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.75 (d, 1H, J=2.2 Hz), 7.59 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 7.31 (d, 1H, J=8.4 Hz), 5.39 (s, 1H), 3.43 (t, 1H, J=5.9 Hz), 3.07 (m, 2H), 2.38 (s, 3H), 1.57 (m, 2H), 0.90 (t, 3H, J=7.5 Hz). 13C NMR (75 MHz, CDCl<sub>3</sub>) δ 149.79, 149.42, 135.79, 133.45, 133.33, 131.34, 130.94, 125.56, 87.10, 46.66, 22.51, 14.01, 11.15.

30        Step D: The compound prepared in Step C (2.76 g, 8.40 mmol) was suspended in ethanol (20 mL), and 15 drops of 10% HCl were added. Upon addition of the HCl significant off-gassing occurred, and at the completion of the off-gassing the reaction mixture was homogeneous.  
35        Isoamyl nitrite (1.35 mL, 10.1 mmol) was then added, and

the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, and then reduced to dryness in vacuo. The residue was purified by column chromatography (gradient elution of 25-50% ethyl acetate/hexanes) to give the final product as purple crystals (2.16 g, 72%), mp 118.5-119.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.30 (bs, 1H), 7.72 (d, 1H, J=2.2 Hz), 7.57 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 7.40 (d, 1H, J=8.5 Hz), 2.72 (m, 2H), 2.70 (s, 3H), 1.45 (m, 2H), 0.82 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 152.98, 149.91, 149.01, 135.40, 134.37, 132.92, 131.23, 131.01, 124.69, 43.90, 22.76, 11.45, 10.95. Anal Calcd. for C<sub>13</sub>H<sub>14</sub>BrClN<sub>4</sub>O: C, 43.66; H, 3.95; N, 15.67. Found: C, 43.85; H, 3.96; N, 15.69.

15

Step E: The compound prepared in Step D (2.06 g, 5.76 mmol) was dissolved in anhydrous pyridine (30 mL) and the solution heated to reflux for 16 hours. The solvent was removed in vacuo and the residue was purified by column chromatography (50% ethyl acetate/hexanes) to recover the product as a brown solid (0.83 g, 42%). This product was used in further reactions directly, however a sample was further purified for analytical purposes by washing briefly with 50% diethyl ether/hexanes to remove a brown oily residue, leaving the final product as an off-white solid, mp 175.5-178.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.69 (bs, 1H), 7.67 (d, 1H, J=1.8 Hz), 7.45 (m, 2H), 2.87 (q, 2H, J=7.5 Hz), 2.45 (s, 3H), 1.38 (t, 3H, J=7.7 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 157.73, 152.93, 136.01, 133.16, 130.80, 130.59, 128.94, 121.14, 120.31, 23.29, 12.91, 12.55.

Step F: The compound prepared in Step E (500 mg, 1.47 mmol) was dissolved in anhydrous dimethylformamide

(15 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 6.1 mL, 3.68 mmol) was added. The solution was heated to 60°C for one hour, then 1-bromobutane (0.63 mL, 5.88 mmol) was added. The reaction was held at 60°C for 4 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (303 mg, 52%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.67 (d, 1H, J=1.8 Hz), 7.44 (m, 2H), 4.01 (t, 2H, J=7.4 Hz), 2.79 (q, 2H, J=7.6 Hz), 2.51 (s, 3H), 1.83 (m, 2H), 1.43 (m, 2H), 1.35 (t, 3H, J=7.5 Hz), 1.00 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.15, 136.17, 133.25, 130.64, 130.53, 128.88, 120.82, 44.89, 33.54, 21.24, 19.99, 13.74, 12.99, 12.80.

#### Example 326

#### 20 Preparation of 4-(3,4-Difluorobenzyl)-5-ethyl-3-methyl-1-(2-chloro-4-bromo) phenylimidazo[4,5-c]pyrazole

The product from Step E, Example 325 (50 mg, 0.15 mmol) was dissolved in anhydrous dimethylformamide (1 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 0.61 mL, 0.37 mmol) was added. The solution was heated to 60°C for one hour, then α-bromo-3,4-difluorotoluene (0.075 mL, 0.59 mmol) was added. The reaction was held at 60°C for 4 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase was washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (33% ethyl

acetate/hexanes) to give the final product as a solid (30 mg, 13%), mp 114-116°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.68 (d, 1H, J=1.5 Hz), 7.46 (m, 2H), 7.21 (m, 1H), 6.95 (m, 2H), 5.21 (s, 2H), 2.79 (q, 2H, J=7.5 Hz), 2.19 (s, 3H), 1.32 (t, 3H, J=7.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.62, 135.96, 133.29, 130.75, 130.61, 128.96, 122.23, 121.13, 118.20, 117.97, 115.54, 115.30, 47.44, 21.38, 12.65, 12.54.

10

Example 327

**Preparation of 4-[1-(1-Ethyl)butane]-5-ethyl-3-methyl-1-(2-chloro-4-bromo) phenylimidazo[4,5-c]pyrazole**

The product from Step E, Example 325 (110 mg, 0.32 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.3 mL, 0.8 mmol) was added. The solution was heated to 60°C for one hour, then 3-bromohexane (211 mg, 1.28 mmol) was added. The reaction was held at 100°C for 64 hours, then cooled to room temperature and diluted with water and diethyl ether. The layers were separated and the organic phase was washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (19 mg, 14%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.67 (t, 1H, J=1.1 Hz), 7.46 (d, 2H, J=1.1 Hz), 4.01 (m, 1H), 2.82 (q, 2H, J=7.5 Hz), 2.53 (s, 3H), 1.86 (m, 4H), 1.35 (t, 3H, J=7.5 Hz), 1.26 (m, 2H), 0.92 (t, 3H, 7.2 Hz), 0.85 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.85, 152.75, 136.08, 133.29, 130.72, 130.66, 130.52, 128.92, 120.84, 119.95, 58.19, 38.40, 29.47, 22.32, 21.94, 19.83, 15.43, 13.87, 12.91, 11.14.

Example 328**Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2-chloro-4-bromo) phenylimidazo[4,5-c]pyrazole**

- 5       The product from Step E, Example 325 (110 mg, 0.32 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.3 mL, 0.8 mmol) was added. The solution was heated to 60°C for one hour, then 2-bromopentane (0.16
- 10   mL, 1.28 mmol) was added. The reaction was held at 100°C for 64 hours, then cooled to room temperature and diluted with water and diethyl ether. The layers were separated and the organic phase was washed with water, dried over anhydrous magnesium sulfate, and reduced to
- 15   dryness *in vacuo*. The residue was purified by column chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (27 mg, 20%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.67 (d, 1H, J=1.4 Hz), 7.45 (m, 2H), 4.31 (m, 1H), 2.83 (q, 2H, J=7.7 Hz), 2.56 (s, 3H), 1.84 (m,
- 20   2H), 1.54 (d, 3H, J=6.6 Hz), 1.33 (t, 3H, J=7.5 Hz), 1.25 (m, 2H), 0.93 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.94, 152.63, 136.07, 133.26, 130.65, 130.60, 130.53, 128.92, 120.85, 120.07, 51.77, 39.77, 22.30, 22.00, 19.87, 15.50, 13.78, 12.98.

25

Example 329**Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-chloro-4-methyl) phenylimidazo[4,5-c]pyrazole**

- Step A: β-Aminocrotonitrile (4.53 g, 0.06 mol) was
- 30   dissolved in 1.0N HCl (90 ml) and treated with 2-chloro-4-methylhydrazine (8.66 g, 0.06 mol). The reaction was allowed to reflux for 6h, cooled, and decanted into a 2 liter beaker. The solution was diluted with water (250 ml) and neutralized with 10% NaOH. The resulting

solution was extracted with Et<sub>2</sub>O (4 x 30 ml) and the combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in-vacuo* to afford 2.29 g (17.2%) of the desired aminopyrazole as a red oil. <sup>1</sup>H NMR (300 Mhz, CDCl<sub>3</sub>) δ 7.34 (m, 2H), 7.19 (m, 1H), 5.46 (s, 1H), 3.56 (bs, 2H), 2.39 (s, 3H), 2.24 (s, 3H).

Step B: The compound prepared in Step A (0.97 g, 4.37 mmol) was suspended in propionic anhydride (2.8 mL, 21.9 mmol) at room temperature and allowed to stir for 16 hours. Ice was added and the reaction stirred for 24 hours. Diethyl ether was added and the phases separated. The organic phase was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate and reduced *in vacuo* to leave a thick oil. This residue was purified by column chromatography (50% ethyl acetate/hexanes) to give the final product as a solid (1.0 g, 85%), mp 115-116.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.33 (m, 2H), 7.21 (d, 1H, J=8.0 Hz), 6.91 (bs, 1H), 6.48 (s, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.27 (q, 2H, J=7.5), 1.14 (t, 3H, J=7.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 149.99, 141.42, 137.22, 132.64, 131.25, 130.72, 129.95, 128.83, 97.88, 29.87, 21.03, 14.05, 9.30. Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>ClN<sub>3</sub>O: C, 60.54; H, 5.82; N, 15.13. Found: C, 60.60; H, 5.79; N, 15.10.

Step C: The compound prepared in Step B (0.94 g, 3.4 mmol) was suspended in anhydrous tetrahydrofuran (20 mL). To this suspension was added borane/THF complex (10.2 mL, 10.2 mmol), and the reaction was refluxed for 1.5 hours. The reaction was cooled to room temperature and excess borane was quenched with 10% NaOH (10 mL) until off-gassing ceased and the reaction was diluted with water and diethyl ether. The layers were separated

and the organic phase was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced in vacuo. This residue was purified by column chromatography (25% ethyl acetate/hexanes) to provide  
5 the final product as a white solid (0.76 g, 85%), mp 100.5-101.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.39 (d, 1H, J=0.8 Hz), 7.31 (d, 1H, J=8.4 Hz), 7.24 (dd, 1H, J=8.1 Hz, J=1.1 Hz), 5.38 (s, 1H), 3.43 (t, 1H, J=5.6 Hz), 3.07 (m, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.55 (m, 2H),  
10 0.89 (t, 3H, J=7.4 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 149.46, 149.13, 142.88, 134.16, 131.77, 131.06, 129.00, 128.69, 86.85, 46.63, 22.54, 21.25, 14.04, 11.14.

Step D: The compound prepared in Step C (0.69 g, 2.62 mmol) was suspended in ethanol (10 mL), and 15 drops of 10% HCl were added. Upon addition of the HCl significant off-gassing occurred, and at the completion of the off-gassing the reaction mixture was homogeneous. Isoamyl nitrite (0.42 mL, 3.14 mmol) was then added, and  
20 the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, and then reduced to dryness in vacuo. The residue was purified by column chromatography (gradient elution of 25-50% ethyl acetate/hexanes) to give the final product as purple  
25 crystals (0.37 g, 48%), mp 83-85°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.28 (bs, 1H), 7.38 (d, 1H, J=8.1 Hz), 7.34 (d, 1H, J=1.9 Hz), 7.20 (dd, 1H, J=8. Hz, J=2.2 Hz), 2.72 (m, 2H), 2.70 (s, 3H), 1.42 (m, 2H), 0.78 (t, 3H, J=7.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 152.51, 142.33,  
30 139.08, 130.52, 129.62, 128.55, 43.63, 22.82, 21.13, 11.45, 10.94. Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>ClN<sub>4</sub>O: C, 57.44; H, 5.85; N, 19.14. Found: C, 57.51; H, 5.83; N, 19.03.

Step E: The compound prepared in Step D (0.34 g, 1.15 mmol) was dissolved in anhydrous pyridine (5 mL)  
35

and the solution heated to reflux for 16 hours. The solvent was removed in vacuo and the residue purified by column chromatography (75% ethyl acetate/hexanes) to afford the product as a brown solid (0.2 g, 60%). This product was used in further reactions directly, however a sample was further purified for analytical purposes by washing briefly with diethyl ether to remove a brown oily residue, leaving the final product as an off-white solid, mp 178-180°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.46 (bs, 1H), 7.39 (d, 1H, J=8.1 Hz), 7.28 (d, 1H, J=1.1 Hz), 7.09 (dd, 1H, J=8.0, J=1.1), 2.80 (q, 2H, J=7.7 Hz), 2.41 (s, 3H), 2.34 (s, 3H), 1.32 (t, 3H, J=7.7 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.73, 153.03, 139.18, 134.15, 130.78, 129.92, 129.74, 128.07, 127.89, 120.13, 23.23, 20.85, 12.86, 12.58. Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>ClN<sub>4</sub>: C, 61.20; H, 5.50; N, 20.39; Cl, 12.90. Found: C, 61.18; H, 5.9; N, 20.34; Cl, 12.78.

Step F: The compound prepared in Step E (50 mg, 0.18 mmol) was dissolved in anhydrous dimethylformamide (1.5 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 0.75 mL, 0.45 mmol) was added. The solution was heated to 60°C for one hour, then 1-bromobutane (0.078 mL, 0.73 mmol) was added. The reaction was held at 60°C for 2 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (45 mg, 75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.41 (d, 1H, J=8.1 Hz), 7.31 (d, 1H, J=1.1 Hz), 7.10 (dd, 1H, J=8.1 Hz, J=1.1 Hz), 4.01 (t, 2H, J=7.5 Hz), 2.79 (q, 2H, J=7.3 Hz), 2.51 (s, 3H), 2.36



(s, 3H), 1.83 (m, 2H), 1.43 (m, 2H), 1.34 (t, 3H, J=7.7 Hz), 0.99 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.98, 152.05, 138.85, 134.31, 130.87, 129.69, 129.64, 128.05, 127.91, 121.98, 44.85, 33.55, 21.26, 20.85, 5 19.99, 13.75, 13.01, 12.87.

#### Example 330

#### Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2-chloro-4-methyl) phenylimidazo[4,5-c]pyrazole

10 The product from Step E, Example 329 (116 mg, 0.42 mmol) was dissolved in anhydrous dimethylformamide (3.5 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.75 mL, 1.05 mmol) was added. The solution  
15 was heated to 60°C for one hour, then 2-bromopentane (0.21 mL, 1.69 mmol) was added. The reaction was held at 100°C for 40 hours, then cooled to room temperature and diluted with water and diethyl ether. The layers  
20 were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness *in vacuo*. The residue was purified by column chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (23 mg, 16%). <sup>1</sup>H NMR (300  
25 MHz, CDCl<sub>3</sub>) δ 7.41 (d, 1H, J=8.1 Hz), 7.32 (s, 1H), 7.12 (d, 1H, J=8.1 Hz) 4.28 (m, 1H), 2.83 (q, 2H, J=7.5 Hz), 2.57 (s, 3H), 2.36 (s, 3H), 1.85 (m, 2H), 1.54 (d, 3H, J=6.6 Hz), 1.33 (t, 3H, J=7.5 Hz), 1.29 (m, 2H), 0.92 (t, 3H, J=7.0 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.77, 152.76, 138.86, 134.23, 130.91, 129.74, 129.67, 128.05,  
30 127.95, 119.73, 51.69, 39.79, 22.31, 22.02, 20.85, 19.87, 15.51, 13.80, 13.07.

Example 331

**Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-chloro-4-trifluoromethyl)phenylimidazo[4,5-c]pyrazole**

5        Step A:  $\beta$ -Aminocrotonitrile (8.39 g, 0.10 mol) was dissolved in 1.0N HCl (350 ml) and treated with 2-chloro-4-trifluoromethylhydrazine (21.52 g, 0.10 mol). The reaction was allowed to reflux for 2.5h, cooled, and decanted into a 2 liter beaker. The solution was  
10        diluted with water (250 ml) and neutralized with 10% NaOH. The resulting precipitate was filtered and dried to constant weight to afford 23.61 g (83%) of the desired aminopyrazole as a white crystalline solid, mp 158.0-160.0°C.  $^1\text{H}$  NMR (300 Mhz,  $\text{CDCl}_3$ )  $\delta$  7.80 (s, 1H),  
15        7.64 (m, 2H), 5.50 (s, 1H), 3.62 (bs, 2H), 2.25 (s, 3H).

Step B: The compound prepared in Step A (4.0 g, 14.5 mmol) was dissolved in propionic anhydride (9.3 mL, 72.5 mmol) at room temperature and was allowed to stir  
20        for 16 hours. Ice was then added and the reaction stirred for 5 hours. The solid product was removed by filtration, washed with water, and dried in vacuo to leave the final product as a yellow solid (3.75 g, 78%),  
          mp 135-138°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (s, 1H), 7.66  
25        (m, 2H), 6.93 (bs, 1H), 6.43 (s, 1H), 2.32 (s, 3H), 2.28 (q, 2H,  $J=7.7$  Hz), 1.13 (t, 3H,  $J=7.7$  Hz).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.92, 151.05, 138.79, 137.13, 132.02, 130.94, 127.64, 125.03, 124.57, 99.79, 29.82, 14.05, 9.27. Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{ClF}_3\text{N}_3\text{O}$ : C, 50.69; H, 3.95; N, 12.67. Found: C, 51.00; H, 4.05; N, 12.27.  
30       

Step C: The compound prepared in Step B (3.63 g, 10.9 mmol) was suspended in tetrahydrofuran (30 mL). To this suspension was added borane/THF complex (32.8 mL,

32.8 mmol), and the reaction refluxed for one hour, then held at room temperature for 16 hours. Excess borane was quenched with 10% NaOH (10 mL) until off-gassing ceased and the reaction was diluted with water and diethyl ether. The layers were separated and the organic phase as washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced in vacuo. This residue was purified by column chromatography (25% ethyl acetate/hexanes) to provide the final product as a white solid (2.73 g, 79%), mp 139-140°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.85 (d, 1H, J=1.9 Hz), 7.72 (dd, 1H, J=8.1 Hz, J=1.5 Hz), 7.60 (d, 1H, J=8.4 Hz), 5.43 (s, 1H), 3.42 (t, 1H, J=5.6 Hz), 3.10 (m, 2H), 2.40 (s, 3H), 1.57 (m, 2H), 0.91 (t, 3H, J=7.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 150.25, 149.43, 135.64, 135.10, 133.08, 127.91, 127.86, 124.95, 124.90, 87.32, 46.70, 22.49, 13.99, 11.14.

Step D: The compound prepared in Step C (2.83 g, 8.91 mmol) was suspended in ethanol (22 mL), and 15 drops of 10% HCl were added. Upon addition of the HCl significant off-gassing occurred, and at the completion of the off-gassing the reaction mixture was homogeneous. Isoamyl nitrite (1.4 mL, 10.7 mmol) was then added, and the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, and then reduced to dryness in vacuo. Hexanes were added to the residual oil and a yellow precipitate formed. This solid was removed by filtration and washed with hexanes, and was later identified as the hydrochloride salt of the desired product (0.51 g, 17%). The filtrate was reduced in vacuo and the residual oil was purified by column chromatography (gradient elution with 25-50% ethyl acetate/hexanes) to give the final product as reddish purple crystals (2.03 g, 66%), mp 95-97°C. <sup>1</sup>H

NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.34 (bs, 1H), 7.83 (s, 1H), 7.70 (m, 2H), 2.73 (s, 3H), 2.70 (m, 2H), 1.45 (m, 2H), 0.81 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  153.31, 149.87, 139.45, 139.01, 134.13, 133.84, 130.65, 127.49, 127.44, 124.92, 124.88, 44.10, 22.73, 11.48, 10.89.  
5 Anal Calcd. for C<sub>14</sub>H<sub>14</sub>ClF<sub>3</sub>N<sub>4</sub>O: C, 48.50; H, 4.08; N, 16.16. Found: C, 48.53; H, 4.11; N, 16.04.

Step E: The compound prepared in Step D (1.92 g, 5.55 mmol) was dissolved in anhydrous pyridine (30 mL) and the solution heated to reflux for 16 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography (50% ethyl acetate/hexanes) to afford the product as a brown solid (0.74 g, 41%). This product was used in further reactions directly, however a sample was further purified for analytical purposes by washing briefly with 50% diethyl ether/hexanes to remove a brown oily residue, leaving the final product as an off-white solid, mp 155.5-158°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.76 (bs, 1H), 7.78 (d, 1H, J=1.5 Hz), 7.76 (d, 1H, J=8.4 Hz), 7.59 (dd, 1H, J=8.4 Hz, J=1.5 Hz), 2.88 (q, 2H, J=7.6 Hz), 2.47 (s, 3H), 1.38 (t, 3H, J=7.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  157.50, 152.94, 139.71, 131.59, 130.85, 130.40, 129.96, 129.39, 128.13, 128.08, 127.74, 124.92, 124.37, 124.33, 121.32, 120.63, 23.28, 12.90, 12.52. Anal. Calcd. for C<sub>14</sub>H<sub>12</sub>ClF<sub>3</sub>N<sub>4</sub>: C, 51.15; H, 3.69; N, 17.04; Cl, 10.79; F, 17.34. Found: C, 51.37; H, 3.77; N, 16.92; Cl, 10.96; F, 16.98.

30 Step F: The compound prepared in Step E (160 mg, 0.49 mmol) was dissolved in anhydrous dimethylformamide (5 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 2.0 mL, 1.22 mmol) was added. The solution was heated to 60°C for one hour, then 1-bromobutane (0.21 mL,

1.96 mmol) was added. The reaction was held at 60°C for 1.5 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous sodium sulfate, and reduced in vacuo. The residue was purified by preparative thin layer chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (83 mg, 44%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.78 (d, 1H, J=1.5 Hz), 7.73 (d, 1H, J=8.4 Hz), 7.58 (dd, 1H, J=8.4 Hz, J=1.5 Hz), 4.00 (t, 2H, J=7.5 Hz), 2.80 (q, 2H, J=7.5 Hz), 2.52 (s, 3H), 1.81 (m, 2H), 1.44 (m, 2H), 1.36 (t, 3H, J=7.7 Hz), 1.00 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.22, 151.95, 139.84, 131.45, 130.06, 129.61, 129.23, 128.24, 128.18, 127.58, 125.02, 124.34, 124.29, 122.62, 44.92, 33.56, 21.24, 19.99, 13.73, 13.01, 12.76

#### Example 332

#### **Preparation of 4-(3,4-Difluorobenzyl)-5-ethyl-3-methyl-1-(2-chloro-4-trifluoromethyl)phenylimidazo[4,5-c]pyrazole**

The product from Step E, Example 331 (160 mg, 0.49 mmol) was dissolved in anhydrous dimethylformamide (5 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 2.0 mL, 1.22 mmol) was added. The solution was heated to 60°C for one hour, then α-bromo-3,4-difluorotoluene (0.25 mL, 1.96 mmol) was added. The reaction was held at 60°C for 2.5 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous sodium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (33% ethyl acetate/hexanes) followed by recrystallization from diethyl ether/hexanes

to give the final product (30 mg, 13%), mp 108-110°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.80 (d, 1H, J=1.5 Hz), 7.75 (d, 1H, J=8.4 Hz), 7.61 (dd, 1H, J=8.4 Hz, J=1.5 Hz), 7.19 (m, 1H), 6.93 (m, 2H), 5.22 (s, 2H), 2.81 (q, 2H, J=7.5 Hz), 2.21 (s, 3H), 1.33 (t, 3H, J=7.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.67, 151.98, 151.69, 139.65, 133.27, 131.52, 130.33, 129.89, 129.33, 128.25, 128.21, 127.71, 124.99, 124.39, 124.35, 122.54, 122.29, 122.20, 118.24, 118.01, 115.55, 115.30, 47.46, 21.39, 12.62, 12.58.

10

#### Example 333

#### **Preparation of 4-[1-(1-Ethyl)butane]-5-ethyl-3-methyl-1-(2-chloro-4-trifluoromethyl)phenylimidazo[4,5-c]pyrazole**

15 The product from Step E, Example 331 (150 mg, 0.45 mmol) was dissolved in anhydrous dimethylformamide (5 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.9 mL, 1.14 mmol) was added. The solution was heated to 60°C for one hour, then 3-bromohexane (300 mg, 20 1.82 mmol) was added. The reaction was held at 80°C for 64 hours, then cooled to room temperature and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in 25 vacuo. The residue was purified by column chromatography (33% ethyl acetate/hexanes) to give the final product as an oil (31 mg, 16%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.77 (m, 2H), 7.59 (dd, 1H, J=8.4 Hz, J=1.5 Hz), 4.02 (m, 1H), 2.83 (q, 2H, J=7.5 Hz), 2.55 (s, 3H), 30 1.85 (m, 4H), 1.36 (t, 3H, J=7.7 Hz), 1.27 (m, 2H), 0.92 (t, 3H, J=7.2 Hz), 0.86 (t, 3H, J=7.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 157.91, 152.73, 139.73, 131.50, 130.06, 129.62, 129.31, 128.26, 128.22, 127.60, 125.03, 124.32,

124.27, 121.43, 120.26, 58.24, 38.41, 37.35, 29.48,  
21.94, 19.83, 15.47, 13.87, 12.88, 11.14.

Example 334

5     **Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2-chloro-4-trifluoromethyl)phenylimidazo[4,5-c]pyrazole**

The product from Step E, Example 501 (150 mg, 0.45 mmol) was dissolved in anhydrous dimethylformamide (5 mL) and  
10     sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.9 mL, 1.14 mmol) was added. The solution was heated to 60°C for one hour, then 2-bromopentane (0.22 mL, 1.82 mmol) was added. The reaction was held at 80°C for 64 hours, then cooled to room temperature and diluted with  
15     water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced to dryness in vacuo. The residue was purified by column chromatography (gradient elution with 33-50% ethyl  
20     acetate/hexanes) to give the final product as an oil (37 mg, 21%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.79 (d, 1H, J=1.5 Hz), 7.75 (d, 1H, J=8.1 Hz), 7.59 (dd, 1H, J=8.4 Hz, J=1.5 Hz), 4.30 (m, 1H), 2.84 (q, 2H, J=7.5 Hz), 2.58 (s, 3H), 1.86 (m, 2H), 1.55 (d, 3H, J=6.6 Hz), 1.34 (t, 3H, J=7.5 Hz), 1.22 (m, 2H), 0.93 (t, 3H, J=7.3 Hz). <sup>13</sup>C  
25     NMR (75 MHz, CDCl<sub>3</sub>) δ 157.01, 139.73, 131.43, 129.31, 128.24, 128.20, 127.63, 124.32, 124.27, 120.40, 51.83, 39.77, 22.29, 21.99, 19.86, 15.52, 13.77, 12.93.

30

Example 353

**Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-chloro-4-methoxy)phenylimidazo[4,5-c]pyrazole**

This compound was obtained as the second eluting compound from the reaction described in Example 355 (see  
35     below) (12 mg, 8%) as a yellow oil. <sup>1</sup>H NMR (300

MHz, CDCl<sub>3</sub>)  $\delta$  7.42 (d, 1H, J=8.8 Hz), 7.03 (d, 1H, J=2.6 Hz), 6.86 (dd, 1H, J=8.8 Hz, J=2.5 Hz), 4.01 (t, 2H, J=7.3 Hz), 3.82 (s, 3H), 2.79 (q, 2H, J=7.7 Hz), 2.51 (s, 3H), 1.73 (m, 2H), 1.44 (m, 2H), 1.34 (t, 3H, J=7.5), 1.00 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>24</sub>ClON<sub>4</sub>): 347.1638. Found: 347.1642.

#### Example 354

##### Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2,4-dimethoxy)phenylimidazo[4,5-c]pyrazole

This compound was obtained as the third eluting compound from the reaction described in Example 520 (29 mg, 19%) as a yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 (d, 1H, J=8.8 Hz), 6.57 (d, 1H, J=2.5 Hz), 6.52 (dd, 1H, J=8.6 Hz, J=2.7 Hz), 3.99 (t, 2H, J=7.3 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 2.77 (q, 2H, J=7.7 Hz), 2.50 (s, 3H), 1.82 (m, 2H), 1.43 (m, 2H), 1.33 (t, 3H, J=7.5 Hz), 0.99 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>27</sub>CO<sub>2</sub>N<sub>4</sub>): 343.2134. Found: 343.2117.

20

#### Example 355

##### Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-methoxy-4-bromo)phenylimidazo[4,5-c]pyrazole

The compound prepared in Step F, Example 325 (178 mg, 0.45 mmol) was dissolved in anhydrous dimethylformamide (2.2 mL). To this solution was added CuBr (9.7 mg, 0.0676 mmol), followed by sodium methoxide (25% in methanol, 0.29 mL, 1.35 mmol). This solution was heated to 155°C for 30 minutes, cooled to room temperature, and diluted with diethyl ether. This solution was shaken with a 20% solution of NH<sub>4</sub>OH in saturated aqueous NH<sub>4</sub>Cl, and the ethereal phase was dried over anhydrous magnesium sulfate and reduced in vacuo to leave a brown oil. This residue was purified by column chromatography (gradient elution with 50-75% ethyl



acetate/hexanes), the first eluting compound being the title product as a yellow oil (27 mg, 15%). Further elution provided Examples 521 and 522, described below. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.37 (m, 1H), 7.15 (m, 2H), 3.99 (t, 2H, J=7.3 Hz), 3.86 (s, 3H), 2.78 (q, 2H, J=7.7 Hz), 2.50 (s, 3H), 1.82 (m, 2H), 1.43 (m, 2H), 1.35 (t, 3H, J=7.5 Hz), 0.99 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>24</sub>BrON<sub>4</sub>): 391.1134. Found: 391.1133.

10

Example 356

**Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2,6-dichloro-4-methoxy)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Example 102 (296 mg, 0.74 mmol) was dissolved in anhydrous dimethylformamide (3.5 mL). To this solution was added CuBr (16 mg, 0.11 mmol), followed by sodium methoxide (25% in methanol, 0.25 mL, 1.11 mmol). This solution was heated to 75°C for 30 minutes, then additional sodium methoxide (0.050 mL, 0.22 mmol) was added and the reaction was heated to 100°C for two hours. The reaction was cooled to room temperature and diluted with diethyl ether. This solution was shaken with a 20% solution of NH<sub>4</sub>OH in saturated aqueous NH<sub>4</sub>Cl, and the ethereal phase was dried over anhydrous magnesium sulfate and reduced in vacuo to leave a yellow oil. This residue was purified by column chromatography (gradient elution with 25-50% ethyl acetate/hexanes), the first eluting compound being the title product as an oil (39 mg, 13%). Further elution provided Example 524, described below. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.95 (s, 2H), 4.28 (m, 1H), 3.82 (s, 3H), 2.82 (q, 2H, J=7.7 Hz), 2.56 (s, 3H), 1.877 (m, 2H), 1.55 (d, 3H, J=7.0 Hz), 1.33 (t, 3H, J=7.5 Hz), 0.92 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>25</sub>Cl<sub>2</sub>ON<sub>4</sub>): 395.1405. Found: 395.1406.

Example 357

**Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2,4-dichloro-6-methoxy)phenylimidazo[4,5-c]pyrazole**

- 5 This compound was obtained as the second eluting compound from the reaction described in Example 523 as an oil (27 mg, 9%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.11 (d, 1H, J=2.2 Hz), 6.90 (d, 1H, J=2.2 Hz), 4.28 (m, 1H), 3.76 (s, 3H), 2.81 (q, 2H, J=7.6 Hz), 1.88 (m, 2H), 1.55 (d, 10 3H, J=7.0 Hz), 1.32 (t, 3H, J=7.5 Hz), 0.92 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>25</sub>Cl<sub>2</sub>ON<sub>4</sub>): 395.1405. Found: 395.1397.

Example 396

- 15 **Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-methyl-4-bromo)phenylimidazo[4,5-c]pyrazole**
- Step A: To 2-methyl-4-bromoaniline (30.0 g, 161 mmol) at 10°C was added concentrated HCl (400 mL), and to this solution was added sodium nitrite (13.4 g, 193 20 mmol) in water (125 mL), maintaining an internal temperature of -10°C during the addition. The reaction was stirred for an hour at 0-5°C, then tin (II) chloride (90.9 g, 403 mmol) in concentrated HCl (395 mL) was added so as to keep the temperature between 5-8°C;
- 25 significant foaming occurred during addition. The orange solid was isolated by filtration and dried to give the hydrazine hydrochloride. This compound was dissolved in 1N HCl (500 mL) and 3-aminocrotonitrile (13.2 g, 161 mmol) was added and the reaction was heated 30 to reflux for 16 hours. It was cooled to room temperature and the supernatant aqueous phase was decanted and neutralized with 50% NaOH, extracted with ethyl acetate, and the organic solution dried over anhydrous magnesium sulfate and reduced *in vacuo* to

leave the crude product. This was purified by column chromatography (gradient elution of 25-50% ethyl acetate/hexanes) to give the product (11.7 g). The residue from the reaction was dissolved in ethyl acetate and extracted with 1N HCl, and this acidic extract was neutralized with 10% NaOH and extracted with ethyl acetate. The organic phase was dried over anhydrous magnesium sulfate and reduced in vacuo to leave the crude product. This was purified by column chromatography (gradient elution of 25-50% ethyl acetate/hexanes) to recover additional pyrazole as a light yellow solid (total of 13.8 g, 32%), mp 89.5-92°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.47 (d, 1H, J=1.8 Hz), 7.41 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 7.18 (d, 1H, J=8.4 Hz), 5.42 (s, 1H), 3.49 (bs, 2H), 2.22 (s, 3H), 2.15 (s, 3H). HRMS Calcd. for M+H (C<sub>11</sub>H<sub>13</sub>BrN<sub>3</sub>): 266.0293. Found: 266.0309. Anal. Calcd. for C<sub>11</sub>H<sub>12</sub>BrN<sub>3</sub>: C, 49.64; H, 4.54; N, 15.79. Found: C, 49.92; H, 4.53; N, 15.67.

Step B: The compound prepared in Step A (13.8 g, 51.7 mmol) was dissolved in propionic anhydride (33.2 mL, 259 mmol) and was allowed to stir for 16 hours at room temperature. Ice was then added and the reaction stirred for 5 hours, then diethyl ether was added and the phases were separated. The organic phase was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate and reduced in vacuo to leave a thick oil. This residue was purified by column chromatography (50% ethyl acetate/hexanes) to give the final product as an off-white solid (13.9 g, 83%), mp 119-121°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.51 (s, 1H), 7.43 (dd, 1H, J=8.0 Hz, J=1.8 Hz), 7.12 (d, 1H, J=8.4 Hz), 6.91 (bs, 1H), 6.47 (s, 1H), 2.29 (s, 3H), 2.25 (q, 2H, J=7.5 Hz), 2.08 (s, 3H), 1.13m (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>17</sub>BrN<sub>3</sub>O): 322.0555. Found: 322.0567. Anal. Calcd.

for  $C_{14}H_{16}BrN_3O$ : C, 52.19; H, 5.02; N, 13.04. Found: C, 51.94; H, 4.98; N, 12.85.

Step C: The compound prepared in Step B (13.9 g, 43.0 mmol) was suspended in tetrahydrofuran (150 mL). To this suspension was added borane/THF complex (129 mL, 129 mmol), and the reaction refluxed for 16 hours. Excess borane was quenched with 10% NaOH (50 mL) until off-gassing ceased and the reaction was diluted with water and diethyl ether. The layers were separated and the organic phase was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced *in vacuo* to leave the product as a white solid (13.7 g, 103%). mp 116-119°C.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.54 (d, 1H,  $J=1.8$  Hz), 7.49 (dd, 1H,  $J=8.5$  Hz,  $J=2.2$  Hz), 7.14 (d, 1H,  $J=8.5$  Hz), 5.38 (s, 1H), 3.38 (t, 1H,  $J=5.7$  Hz), 3.05 (q, 2H,  $J=6.7$  Hz), 2.37 (s, 3H), 2.03 (s, 3H), 1.53 (m, 2H), 0.88 (t, 3H,  $J=7.3$  Hz). HRMS Calcd. for  $M+H$  ( $C_{14}H_{19}BrN_3$ ): 308.0763. Found: 308.0754.

Step D: The compound prepared in Step C (13.6 g, 44.3 mmol) was suspended in ethanol (110 mL), and one mL of 10% HCl was added. Upon addition of the HCl significant off-gassing occurred, and at the completion of the off-gassing the reaction mixture was homogeneous. Isoamyl nitrite (7.1 mL, 53.2 mmol) was added, and the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, and then a few drops of triethylamine were added to neutralize the HCl. The reaction was reduced to dryness *in vacuo* and the residue was dissolved in dichloromethane and the insoluble triethylamine hydrochloride was removed by filtration. The reaction was reduced to dryness again and diethyl ether was added, causing a precipitate to form. This solid was isolated by filtration and rinsed

with hexanes to leave the product as a purple solid (11.4 g, 76%), mp 120-121.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.11 (bs, 1H), 7.50 (d, 1H, J=1.8 Hz), 7.45 (dd, 1H, J=8.5 Hz, J=1.8 Hz), 7.21 (d, 1H, J=8.4 Hz), 3.10 (q, 1H, J=7.3 Hz), 2.70 (s, 3H), 2.66 (m, 2H), 2.17 (s, 3H), 1.42 (m, 3H), 0.79 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>18</sub>BrN<sub>4</sub>O): 337.0664. Found: 337.0662. Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>BrN<sub>4</sub>O: C, 49.86; H, 5.08; N, 16.61. Found: C, 49.90; H, 4.92; N, 16.50.

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Step E: The compound prepared in Step D (11.3 g, 33.5 mmol) was dissolved in anhydrous pyridine (100 mL) and the solution heated to reflux for 16 hours. The solvent was removed in vacuo and the residue purified by column chromatography (50% ethyl acetate/hexanes) to afford the product as a tan solid (7.3 g, 68%) mp 136-138°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.81 (bs, 1H), 7.44 (m, 1H), 7.35 (m, 2H), 2.83 (q, 2H, J=7.7 Hz), 2.43 (s, 3H), 2.37 (s, 3H), 1.36 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>16</sub>BrN<sub>4</sub>): 319.0559. Found: 319.0555. Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>BrN<sub>4</sub>: C, 52.68; H, 4.75; N, 17.55. Found: C, 52.53; H, 4.61; N, 17.42.

Step F: The compound prepared in Step E (130 mg, 0.41 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.7 mL, 1.02 mmol) was added. The solution was heated to 60°C for one hour, then 1-bromobutane (0.17 mL, 1.63 mmol) was added. The reaction was held at 60°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (15% ethyl

acetate/hexanes) to give the final product as an oil (120 mg, 79%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 (m, 1H), 7.36 (m, 2H), 4.01 (t, 2H, J=7.5 Hz), 2.78 (q, 2H, J=7.5 Hz), 2.49 (s, 3H), 2.38 (s, 3H), 1.82 (m, 2H), 1.43 (m, 2H), 1.35 (t, 3H, J=7.5 Hz), 1.00 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>24</sub>BrN<sub>4</sub>): 375.1185. Found: 375.1185. Anal. Calcd. for C<sub>18</sub>H<sub>23</sub>BrN<sub>4</sub>: C, 57.60; H, 6.19; N, 14.93. Found: C, 57.63; H, 6.00; N, 14.74.

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Example 397

**Preparation of 4-(3,4-Difluorobenzyl)-5-ethyl-3-methyl-1-(2-methyl-4-bromo)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Step E, Example 396, (130 mg, 0.41 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.7 mL, 1.02 mmol) was added. The solution was heated to 60°C for one hour, then α-bromo-3,4-difluorotoluene (0.21 mL, 1.63 mmol) was added. The reaction was held at 60°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to give the final product as a crystalline solid (125 mg, 69%), mp 127-129°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.45 (s, 1H), 7.37 (m, 2H), 7.17 (m, 1H), 6.90 (m, 2H), 5.21 (s, 2H), 2.78 (q, 2H, J=7.5 Hz), 2.9 (s, 3H), 1.57 (s, 3H), 1.32 (t, 3H, J=7.7 Hz). HRMS Calcd. for M+H (C<sub>21</sub>H<sub>20</sub>BrF<sub>2</sub>N<sub>4</sub>): 445.0840. Found: 445.0845. Anal. Calcd. for C<sub>21</sub>H<sub>19</sub>BrF<sub>2</sub>N<sub>4</sub>: C, 56.64; H, 4.30; N, 12.58. Found: C, 56.46; H, 4.21; N, 12.22.

Example 398

**Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2-methyl-4-bromo)phenylimidazo[4,5-c]pyrazole**

- 5        The compound prepared in Step E, Example 396, (5.38 g, 16.8 mmol) was dissolved in anhydrous dimethylformamide (170 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 70.2 mL, 42.1 mmol) was added. The solution was heated to 60°C.
- 10       for one hour, then 2-bromopentane (8.3 mL, 67.2 mmol) was added. The reaction was held at 80°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous
- 15       magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (gradient elution with 10-50% ethyl acetate/hexanes) to give the final product as an oil (1.68 g, 26%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (m, 1H), 7.36 (m, 2H), 4.28 (m, 1H), 2.83 (q, 2H, J=7.5 Hz), 2.55 (s, 3H), 2.39 (s, 3H), 1.85 (m, 2H),
- 20       1.54 (d, 3H, J=6.6 Hz), 1.34 (t, 3H, J=7.5 Hz), 1.20 (m, 2H), 0.92 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>26</sub>BrN<sub>4</sub>): 389.1341. Found: 389.1341. Anal. Calcd. for C<sub>19</sub>H<sub>25</sub>BrN<sub>4</sub>: C, 58.61; H, 6.47; N, 14.39. Found: C,
- 25       58.88; H, 6.36; N, 14.33.

Example 399

**Preparation of 4-[1-(1-Ethyl)butane]-5-ethyl-3-methyl-1-(2-methyl-4-bromo)phenylimidazo[4,5-c]pyrazole**

- 30       The compound prepared in Step E, Example 396, (319 mg, 1.0 mmol) was dissolved in anhydrous dimethylformamide (10 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 4.2 mL, 2.5

mmol) was added. The solution was heated to 60°C for one hour, then 3-bromohexane (660 mg, 4.0 mmol) was added. The reaction was held at 80°C for 16 hours, cooled to room temperature, and diluted with water and diethyl  
5 ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to give the final product as an oil (37 mg, 9%). <sup>1</sup>H NMR  
10 (300 MHz, CDCl<sub>3</sub>) δ 7.44 (m, 1H), 7.37 (m, 2H), 4.02 (m, 1H), 2.80 (q, 2H, J=7.5 Hz), 2.52 (s, 3H), 2.38 (s, 3H), 1.83 (m, 4H), 1.35 (t, 3H, J=7.5 Hz), 1.26 (m, 2H), 0.91 (t, 3H, J=7.3 Hz), 0.84 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>20</sub>H<sub>28</sub>BrN<sub>4</sub>): 403.1498. Found: 403.1494.

15

#### Example 400

#### **Preparation of 4-(n-Butyl)-5-ethyl-3-methyl-1-(2-trifluoromethyl-4-bromo)phenylimidazo[4,5-c]pyrazole**

20 Step A: To 2-trifluoromethyl-4-bromoaniline (38.4 g, 160 mmol) was added concentrated HCl (400 mL), and to this solution was cooled to 5°C. To this was added sodium nitrite (13.25 g, 192 mmol) in water (125 mL), maintaining an internal temperature of -10°C with  
25 additional cooling. The reaction was stirred for an hour at 0-5°C, then tin (II) chloride (95.0 g, 400 mmol) in concentrated HCl (400 mL) was added so as to keep the temperature between 5-8°C; significant foaming occurred during addition. The orange solid was recovered by  
30 filtration and dried to give the hydrazine hydrochloride (34.9 g, 120 mmol, 75%). This compound was suspended in 1N HCl (500 mL), 3-aminocrotonitrile (9.84 g, 120 mmol) was added and the reaction heated to reflux for 3 hours.



It was cooled to room temperature and the supernatant aqueous phase was decanted, filtered to remove a small amount of dark solids, and neutralized with 10% NaOH to give a fine off-white solid. This solid was recovered  
5 by filtration and dried to give the product (27.4 g, 71%), mp 117-119°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.94 (d, 1H, J=2.2 Hz), 7.80 (dd, 1H, J=8.4 Hz, J=2.2 Hz), 7.33 (d, 1H, J=8.4 Hz), 5.44 (s, 1H), 3.44 (bs, 1H), 2.21 (s, 3H). HRMS Calcd. for M+H (C<sub>11</sub>H<sub>10</sub>BrF<sub>3</sub>N<sub>3</sub>): 320.0011. Found:  
10 320.0005. Anal. Calcd. for C<sub>11</sub>H<sub>9</sub>BrF<sub>3</sub>N<sub>3</sub>: C, 41.27; H, 2.83; N, 13.13. Found: C, 41.33; H, 2.56; N, 12.96.

Step B: The compound prepared in Step A (27.3 g, 85.4 mmol) was dissolved in propionic anhydride (54.8 mL, 427 mmol) and was allowed to stir for 2 hours at  
15 room temperature. Ice was then added and the reaction stirred for 16 hours, providing the product as a solid. The product was isolated by filtration and dried to leave an off-white solid (29.8 g, 93%), mp 165.5-167.5°C.  
20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.94 (d, 1H, J=2.2 Hz), 7.80 (dd, 1H, J=8.2 Hz, J=2.0 Hz), 7.33 (d, 1H, J=8.2 Hz), 6.86 (bs, 1H), 6.34 (s, 1H), 2.29 (s, 3H), 2.21 (q, 2H, J=7.5 Hz), 1.08 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>14</sub>BrF<sub>3</sub>ON<sub>3</sub>): 376.0273. Found: 376.0267. Anal. Calcd.  
25 for C<sub>14</sub>H<sub>13</sub>BrF<sub>3</sub>ON<sub>3</sub>: C, 44.70; H, 3.48; N, 11.17. Found: C, 44.47; H, 3.27; N, 11.02.

Step C: The compound prepared in Step B (29.8 g, 79.1 mmol) was suspended in anhydrous tetrahydrofuran  
30 (220 mL). To this suspension was added borane/THF complex (237 mL, 237 mmol), and the reaction refluxed for 16 hours. Excess borane was quenched with 10% NaOH (100 mL) until off-gassing ceased, and the reaction was filtered through Celite. Diethyl ether was added and  
35 the layers were separated, the organic phase was washed

with saturated sodium chloride, dried over anhydrous magnesium sulfate, and reduced *in vacuo* to leave the product as a white solid (28.4 g, 99%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.94 (d, 1H, J=2.2 Hz), 7.79 (dd, 1H, J=8.4 Hz, J=2.2 Hz), 5.31 (s, 1H), 3.10 (bs, 1H), 3.01 (m, 2H), 2.23 (s, 3H), 1.54 (m, 2H), 0.90 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>16</sub>BrF<sub>3</sub>N<sub>3</sub>): 362.0480. Found: 362.0470.

10        Step D: The compound prepared in Step C (28.3 g, 78.1 mmol) was suspended in ethanol (200 mL), and one mL of 10% HCl was added. Upon addition of the HCl significant off-gassing occurred, and at the completion of the off-gassing the reaction mixture was homogeneous.

15        Isoamyl nitrite (12.6 mL, 93.8 mmol) was then added, and the solution darkened upon addition. The solution was stirred at room temperature for 16 hours, and then a few drops of triethylamine were added to neutralize the HCl. The reaction was reduced to dryness *in vacuo* and the

20        residue was dissolved in dichloromethane and the insoluble triethylamine hydrochloride was removed by filtration. The reaction was again reduced to dryness and hexanes was added, causing a red precipitate to form. This solid was isolated by filtration and rinsed

25        with hexanes to leave the product as a red solid (18.2 g, 60%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.34 (bs, 1H), 7.97 (d, 1H, J=1.8 Hz), 7.85 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 7.38 (d, 8.5 Hz), 2.70 (s, 3H), 2.65 (m, 2H), 1.44 (m, 2H), 0.82 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>15</sub>BrON<sub>4</sub>): 391.0382. Found: 391.0380. Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>BrON<sub>4</sub>: C, 42.98; H, 3.62; N, 14.32. Found: C, 3.22; H, ; N, 14.09.

30       

Step E: The compound prepared in Step D (18.1 g, 46.2 mmol) was dissolved in anhydrous pyridine (200 mL)

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and the solution heated to reflux for 16 hours. The solvent was removed in vacuo and the residue purified by column chromatography (gradient elution with 25-50% ethyl acetate/hexanes) to afford the product as a tan solid (13.1 g, 76%) mp 158-160.5°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.65 (bs, 1H), 7.92 (d, 1H, J=2.2 Hz), 7.73 (dd, 1H, J=8.8 Hz, J=2.2 Hz), 7.52 (d, 1H, J=8.4 Hz), 2.85 (q, 2H, J=7.5 Hz), 2.43 (s, 3H), 1.38 (t, 3H, J=7.7 Hz). HRMS Calcd. for M+H (C<sub>14</sub>H<sub>13</sub>BrN<sub>4</sub>): 373.0276. Found: 373.0281. Anal. Calcd. for C<sub>14</sub>H<sub>12</sub>BrN<sub>4</sub>: C, 45.06; H, 3.24; N, 15.01. Found: C, 44.70; H, 3.00; N, 14.59.

Step F: The compound prepared in Step E (153 mg, 0.41 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.7 mL, 1.02 mmol) was added. The solution was heated to 60°C for one hour, then 1-bromobutane (0.17 mL, 1.63 mmol) was added. The reaction was held at 60°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (gradient elution with 15-25% ethyl acetate/hexanes) to give the final product as a crystalline solid (68 mg, 39%), mp 78-80°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.91 (d, 1H, J=2.2 Hz), 7.72 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 7.55 (d, 1H, J=8.4 Hz), 4.01 (t, 2H, J=7.3 Hz), 2.78 (q, 2H, J=7.5 Hz), 2.48 (s, 3H), 1.83 (m, 2H), 1.42 (m, 2H), 1.35 (t, 3H, J=7.7 Hz), 1.00 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>18</sub>H<sub>21</sub>BrF<sub>3</sub>N<sub>4</sub>): 429.0902. Found: 429.0894. Anal. Calcd. for C<sub>18</sub>H<sub>20</sub>BrF<sub>3</sub>N<sub>4</sub>: C, 50.36; H, 4.71; N, 13.05. Found: C, 50.70; H, 4.58; N, 12.91.

Example 401

**Preparation of 4-(3,4-Difluorobenzyl)-5-ethyl-3-methyl-1-(2-trifluoromethyl-4-bromophenylimidazo[4,5-c]pyrazole**

- 5        The compound prepared in Step E, Example 400, (153 mg, 0.41 mmol) was dissolved in anhydrous dimethylformamide (4 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 1.7 mL, 1.02 mmol) was added. The solution was heated to 60°C for one
- 10    hour, then  $\alpha$ -bromo-3,4-difluorotoluene (0.21 mL, 1.63 mmol) was added. The reaction was held at 60°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over
- 15    anhydrous magnesium sulfate, and reduced *in vacuo*. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to give the final product as a crystalline solid (74 mg, 36%), mp 105-107°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (d, 1H, J=2.2 Hz), 7.75 (dd, 1H, J=8.8 Hz, J=2.2 Hz), 7.57 (d, 1H, J=8.4 Hz), 7.18 (m, 1H), 6.90 (m, 2H), 5.21 (s, 2H), 2.77 (q, 2H, J=7.5 Hz), 2.18 (s, 3H), 1.32 (t, 3H, J=7.7 Hz). HRMS Calcd. for M+H (C<sub>21</sub>H<sub>17</sub>BrF<sub>5</sub>N<sub>4</sub>): 499.0557. Found: 499.0558. Anal. Calcd. for C<sub>21</sub>H<sub>16</sub>BrF<sub>5</sub>N<sub>4</sub>: C, 50.52; H, 3.23; N, 11.22.
- 25    Found: C, 50.98; H, 3.19; N, 11.01.

Example 402

**Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2-trifluoromethyl-4-bromo)phenylimidazo[4,5-c]pyrazole**

- 5       The compound prepared in Step E, Example 400, (3.4 g, 9.16 mmol) was dissolved in anhydrous dimethylformamide (100 mL) and sodium bis(trimethylsilyl)amide (0.6 M in toluene, 38.2 mL, 22.9 mmol) was added. The solution was heated to 60°C.
- 10       for one hour, then 2-bromopentane (4.5 mL, 36.6 mmol) was added. The reaction was held at 80°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous
- 15       magnesium sulfate, and reduced in vacuo. The residue was purified by column chromatography (gradient elution with 10-20% ethyl acetate/hexanes) to give the final product as a crystalline solid (829 mg, 20%), mp 51-53°C.
- 20       <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.92 (d, 1H, J=2.2 Hz), 7.73 (dd, 1H, J=8.4 Hz, J=2.2 Hz), 7.58 (d, 1H, J=8.4 Hz), 4.29 (m, 1H), 2.81 (q, 2H, J=7.5 Hz), 2.53 (s, 3H), 1.85 (m, 2H), 1.54 (d, 3H, J=6.6 Hz), 1.34 (t, 3H, J=7.5 Hz), 0.92 (t, 3H, J=7.3 Hz). HRMS Calcd. for M+H (C<sub>19</sub>H<sub>23</sub>BrF<sub>3</sub>N<sub>4</sub>): 443.1059. Found: 443.1064. Anal. Calcd. for C<sub>19</sub>H<sub>22</sub>BrF<sub>3</sub>N<sub>4</sub>: C, 51.48; H, 5.00; N, 12.64. Found: C, 51.84; H, 4.99; N, 12.56.

Example 403

30       **Preparation of 5-Ethyl-4-[1-(1-ethyl)butane]-3-methyl-1-(2-trifluoromethyl-4-bromo)phenylimidazo[4,5-c]pyrazole**

The compound prepared in Step E, Example 400, (373 mg, 1.0 mmol) was dissolved in anhydrous dimethylformamide (10 mL) and sodium

bis(trimethylsilyl)amide (0.6 M in toluene, 4.2 mL, 2.5 mmol) was added. The solution was heated to 60°C for one hour, then 3-bromohexane (660.mg, 4.0 mmol) was added. The reaction was held at 80°C for 16 hours, cooled to room temperature, and diluted with water and diethyl ether. The layers were separated and the organic phase washed with water, dried over anhydrous magnesium sulfate, and reduced *in vacuo*. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to give the final product as an oil (50 mg, 11%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.91 (d, 1H, J=2.2 Hz), 7.73 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 7.61 (d, 1H, J=8.8 Hz), 4.00 (m, 1H), 2.80 (q, 2H, J=7.5 Hz), 2.51 (s, 3H), 1.83 (m, 4H), 1.35 (t, 3H, J=7.5 Hz), 1.23 (m, 2H), 0.91 (t, 3H, J=7.3 Hz), 0.83 (t, 3H, J=7.5 Hz). HRMS Calcd. for M+H (C<sub>20</sub>H<sub>25</sub>BrF<sub>3</sub>N<sub>4</sub>): 457.1215. Found: 457.1223.

#### Example 408

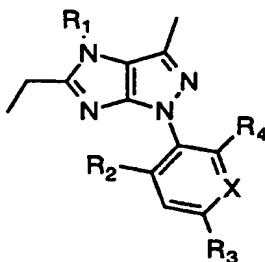
#### Preparation of 5-Ethyl-4-[1-(1-methyl)butane]-3-methyl-1-(2-methyl-4-acetyl)phenylimidazo[4,5-c]pyrazole

The compound prepared in Example 396 (492 mg, 1.26 mmol) was dissolved in anhydrous toluene (5 mL) and dichlorobis (triphenylphosphine)palladium(II) (18 mg, 0.025 mmol) was added, followed by tributyl(1-ethoxyvinyl)tin (548 mg, 1.52 mmol), and the solution was heated to reflux for 2.5 hours. The reaction was cooled to room temperature and quenched with 1N HCl (10 mL) and diethyl ether. After stirring for 30 minutes the layers were separated and the organic phase was washed with saturated aqueous sodium chloride, filtered through Celite, dried over anhydrous magnesium sulfate and reduced to dryness *in vacuo*. The crude product was purified by column chromatography (gradient elution with 10-20% ethyl acetate/hexanes) to give the final product

as a yellow oil (225 mg, 51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.91 (m, 1H), 7.85 (dd, 1H, J=8.4 Hz, J=1.8 Hz), 7.68 (d, 1H, J=8.1 Hz), 4.30 (m, 1H), 2.83 (q, 2H, J=7.5 Hz), 2.61 (s, 3H), 2.57 (s, 3H), 2.56 (s, 3H), 1.86 (m, 2H),  
5 1.54 (d, 3H, J=6.6 Hz), 1.35 (t, 3H, J=7.5 Hz), 1.21 (t, 3H, J=7.1 Hz). HRMS Calcd. for M+H (C<sub>21</sub>H<sub>29</sub>ON<sub>4</sub>): 353.2341. Found: 353.2344. Anal. Calcd. for C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>O: C, 71.56; H, 8.02; N, 15.90. Found: C, 71.39; H, 7.97; N, 15.55.

- 10        The Examples in Table 3 may be prepared as amply exemplified above for the preparation of Examples 325-334, 353-357, 396-403, and 408.

TABLE 3



Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	X	mp °C
262	CH <sub>2</sub> C(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	Me	Me	C	Oil, MS
263	benzyl	Me	Me	Me	C	97-98
264	n-butyl	Me	Me	Me	C	81-83
265	2-phenylbenzyl	Me	Me	Me	C	
266	4-phenylbenzyl	Me	Me	Me	C	
267	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	Me	Me	Me	C	
268	CH <sub>2</sub> C(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	Me	Me	N	
269	benzyl	Me	Me	Me	N	
270	n-butyl	Me	Me	Me	N	
271	4-fluorobenzyl	Br	iPr	H	C	107-108
272	2-phenylbenzyl	Br	iPr	H	C	Oil, MS
273	4-phenylbenzyl	Br	iPr	H	C	135-136
274	n-pentyl	Br	iPr	H	C	132-135
275	benzyl	Br	iPr	H	C	Oil, MS
276	n-butyl	Br	iPr	H	C	76-69
277	CH <sub>2</sub> cPr	Br	iPr	H	C	Oil, MS
278	CH <sub>2</sub> CH(Et) <sub>2</sub>	Br	iPr	H	C	Oil, MS
279	CH(Et) <sub>2</sub>	Br	iPr	H	C	Oil, MS
280	CH <sub>2</sub> CH <sub>2</sub> CH(Me) <sub>2</sub>	Br	iPr	H	C	Oil, MS
281	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	iPr	H	C	Oil, MS
282	CH(Me)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	iPr	H	C	Oil, MS
283	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	Br	iPr	H	C	
284	CH <sub>2</sub> CH <sub>2</sub> SCH <sub>2</sub> CH <sub>3</sub>	Br	iPr	H	C	
285	4-picolyl	Br	iPr	H	C	
286	CH(cPr) <sub>2</sub>	Br	iPr	H	C	
287	CH(ethyl)n-butyl	Br	iPr	H	C	
288	CH(CH <sub>2</sub> OMe) <sub>2</sub>	Br	iPr	H	C	
289	benzyl	Br	OMe	OMe	C	
290	n-butyl	Br	OMe	OMe	C	
291	4-fluorobenzyl	Br	OMe	OMe	C	
292	2-phenylbenzyl	Br	OMe	OMe	C	
293	4-phenylbenzyl	Br	OMe	OMe	C	
294	n-pentyl	Br	OMe	OMe	C	
295	CH(cPr) <sub>2</sub>	Br	OMe	OMe	C	



TABLE 3 (Continued)

Ex.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	X	mp °C
296	benzyl	Br	Cl	Cl	C	125-127
297	n-butyl	Br	Cl	Cl	C	111-112
298	CH <sub>2</sub> cPr	Br	Cl	Cl	C	128-129
299	CH <sub>2</sub> CH(ethyl) <sub>2</sub>	Br	Cl	Cl	C	127-128
300	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Br	Cl	Cl	C	88-89
301	4-fluorobenzyl	Br	Cl	Cl	C	110-113
302	4-phenylbenzyl	Br	Cl	Cl	C	131-134
303	n-pentyl	Br	Cl	Cl	C	135-136
304	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	Cl	Cl	C	116-118
305	CH(Me)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	Cl	Cl	C	Oil, MS
306	benzyl	Br	Cl	Br	C	117-124
307	n-butyl	Br	Cl	Br	C	112-113
308	CH <sub>2</sub> cPr	Br	Cl	Br	C	122-123
309	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Br	Cl	Br	C	124-126
310	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Br	Cl	Br	C	67-69
311	4-fluorobenzyl	Br	Cl	Br	C	Oil, MS
312	4-phenylbenzyl	Br	Cl	Br	C	124-125
313	n-pentyl	Br	Cl	Br	C	124-125
314	n-butyl	Cl	Br	Cl	C	111-112
315	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Br	Cl	C	115-116
316	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Cl	Br	Cl	C	142-144
317	benzyl	Cl	Br	Cl	C	136-137
318	3,4-difluorobenzyl	Cl	Br	Cl	C	136-138
319	CH <sub>2</sub> -(2-tetrahydropyran)	Cl	Br	Cl	C	136-138
320	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Br	Cl	C	132-133
321	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Br	Cl	C	Oil, MS
322	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Br	Cl	C	95-98
323	n-butyl	Cl	CN	H	C	163-165
324	n-butyl	Cl	CN	CN	C	151-153
325	n-butyl	Cl	Br	H	C	Oil, MS
326	3,4-difluorobenzyl	Cl	Br	H	C	114-116
327	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Br	H	C	Oil, MS
328	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Br	H	C	Oil, MS
329	n-butyl	Cl	Me	H	C	Oil, MS
330	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Me	H	C	Oil, MS
331	n-butyl	Cl	CF <sub>3</sub>	H	C	Oil, MS
332	3,4-difluorobenzyl	Cl	CF <sub>3</sub>	H	C	108-110
333	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	CF <sub>3</sub>	H	C	Oil, MS
334	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	CF <sub>3</sub>	H	C	Oil, MS
335	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Cl	H	C	Oil, MS
336	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Cl	H	C	105-107

TABLE 3 (Continued)

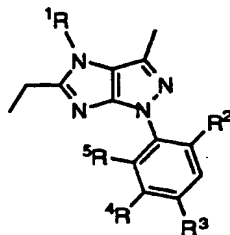
Ex.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	X	mp °C
337	n-butyl	Cl	Cl	H	C	Oil, MS
338	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Cl	H	C	Oil, MS
339	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Cl	Cl	H	C	Oil, MS
340	benzyl	Cl	Cl	H	C	Oil, MS
341	3,4-difluorobenzyl	Cl	Cl	H	C	124-125
342	CH <sub>2</sub> -(2-tetrahydropyran)	Cl	Cl	H	C	100-101
343	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Cl	H	C	Oil, MS
344	n-butyl	Et	Br	Et	C	54-55
345	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Et	Br	Et	C	Oil, MS
346	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Et	Br	Et	C	Oil, MS
347	benzyl	Et	Br	Et	C	Oil, MS
348	3,4-difluorobenzyl	Et	Br	Et	C	Oil, MS
349	CH <sub>2</sub> -(2-tetrahydropyran)	Et	Br	Et	C	Oil, MS
350	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Et	Br	Et	C	70-72
351	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Et	Br	Et	C	91-93
352	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Et	Br	Et	C	82-84
353	n-butyl	Cl	OMe	H	C	Oil, MS
354	n-butyl	OMe	OMe	H	C	Oil, MS
355	n-butyl	OMe	Br	H	C	Oil, MS
356	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	OMe	Cl	C	Oil, MS
357	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	OMe	Cl	Cl	C	Oil, MS
358	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	OMe	H	C	
359	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	OMe	Cl	C	
360	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Br	OMe	OMe	C	
361	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	OMe	H	C	
362	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	OMe	Cl	C	
363	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	OMe	OMe	N	
364	benzyl	H	OMe	OMe	N	
365	n-butyl	H	OMe	OMe	N	
366	CH <sub>2</sub> cPr	H	OMe	OMe	N	
367	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	H	OMe	OMe	N	
368	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	OMe	OMe	N	
369	3,4-difluorobenzyl	H	OMe	OMe	N	
370	CH <sub>2</sub> cPr	Me	Me	Me	N	
371	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	Me	Me	N	
372	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	Me	Me	N	
373	3,4-difluorobenzyl	Me	Me	Me	N	
374	CH <sub>2</sub> cPr	Me	Me	H	N	
375	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Me	Me	H	N	
376	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	NMe <sub>2</sub>	H	N	
377	3,4-difluorobenzyl	Me	NMe <sub>2</sub>	H	N	

TABLE 3 (Continued)

Ex.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	X	mp °C
378	n-pentyl	Et	Me	Et	C	
379	benzyl	Et	Me	Et	C	
380	n-pentyl	H	Me	Me	N	
381	benzyl	H	Me	Me	N	
382	n-pentyl	H	NMe <sub>2</sub>	Me	N	
383	benzyl	H	NMe <sub>2</sub>	Me	N	
384	n-pentyl	CF <sub>3</sub>	NMe <sub>2</sub>	H	C	
385	benzyl	CF <sub>3</sub>	NMe <sub>2</sub>	H	C	
386	n-pentyl	Me	NMe <sub>2</sub>	H	C	
387	benzyl	Me	NMe <sub>2</sub>	H	C	
388	n-pentyl	Br	NMe <sub>2</sub>	H	C	
389	benzyl	Br	NMe <sub>2</sub>	H	C	
390	n-pentyl	Br	iPr	OMe	C	
391	benzyl	Br	iPr	OMe	C	
392	n-pentyl	Br	SMe	H	C	
393	benzyl	Br	SMe	H	C	
394	n-pentyl	Br	SOMe	H	C	
395	benzyl	Br	SO <sub>2</sub> Me	H	C	
396	n-butyl	Me	Br	H	C	Oil, MS
397	3,4-difluorobenzyl	Me	Br	H	C	127-129
398	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	Br	H	C	Oil, MS
399	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	Br	H	C	Oil, MS
400	n-butyl	CF <sub>3</sub>	Br	H	C	78-80
401	3,4-difluorobenzyl	CF <sub>3</sub>	Br	H	C	105-107
402	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub>	Br	H	C	51-53
403	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub>	Br	H	C	Oil, MS
404	n-butyl	Br	Me	F	C	
405	3,4-difluorobenzyl	Br	Me	H	C	
406	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	OMe	Me	H	C	
407	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	COMe	Me	H	C	
408	n-butyl	Me	COMe	H	C	
409	3,4-difluorobenzyl	Me	COMe	Me	C	
410	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	COMe	H	C	
411	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	COMe	Cl	C	
412	n-butyl	Cl	Ph	H	C	
413	3,4-difluorobenzyl	Cl	Ph	OMe	C	
414	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	CO <sub>2</sub> Me	Cl	C	
415	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	OCOMe	Cl	C	

Examples 416-452 given in TABLE 4 may be prepared from compounds of formula  $R^3(NH_2)C=C(CN)H$  where  $R^3$  is Me and the appropriate hydrazine of formula  $R^4NHNH_2$ , where  $R^4$  corresponds to the substitutions exemplified in Table 4 to give initially compounds of formula (III). Conversion to compounds of formula (I) may then follow the preparation detailed for Examples 38 and 164.

TABLE 4

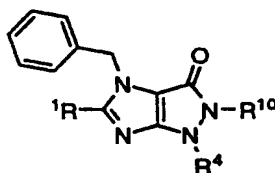


Ex.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	mp °C
416	n-butyl	Cl	H	Cl	H	Oil, MS
417	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	H	Cl	H	Oil, MS
418	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Cl	H	Cl	H	Oil, MS
419	benzyl	Cl	H	Cl	H	113-114
420	3,4-difluorobenzyl	Cl	H	Cl	H	Oil, MS
421	CH <sub>2</sub> -(2-tetrahydropyran)	Cl	H	Cl	H	125-126
422	CH(CH <sub>2</sub> CH <sub>3</sub> )(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )	Cl	H	Cl	H	Oil, MS
423	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	H	Cl	H	Oil, MS
424	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	H	Cl	H	Oil, MS
425	n-butyl	H	Cl	Cl	Cl	Oil, MS
426	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	Cl	Cl	Cl	Oil, MS
427	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	H	Cl	Cl	Cl	Oil, MS
428	benzyl	H	Cl	Cl	Cl	Oil, MS
429	3,4-difluorobenzyl	H	Cl	Cl	Cl	Oil, MS
430	CH <sub>2</sub> -(2-tetrahydropyran)	H	Cl	Cl	Cl	Oil, MS
431	n-butyl	Cl	Cl	Cl	H	Oil, MS
432	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Cl	Cl	H	Oil, MS
433	CH <sub>2</sub> CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	Cl	Cl	Cl	H	Oil, MS
434	benzyl	Cl	Cl	Cl	H	153-155
435	3,4-difluorobenzyl	Cl	Cl	Cl	H	Oil, MS
436	CH <sub>2</sub> -(2-tetrahydropyran)	Cl	Cl	Cl	H	Oil, MS
437	CH(CH <sub>2</sub> CH <sub>3</sub> )(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> )	Cl	Cl	Cl	H	Oil, MS
438	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Cl	Cl	H	Oil, MS
439	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Cl	Cl	H	Oil, MS
440	benzyl	Br	Me	F	H	
441	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Br	Me	F	H	
442	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Me	Br	F	H	
443	benzyl	Me	Me	F	Me	
444	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	Me	F	Me	
445	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Cl	F	H	
446	benzyl	Me	Br	Cl	H	
447	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	Me	Me	H	
448	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Cl	Me	Me	H	
449	benzyl	Cl	Br	Me	H	
450	CH(CH <sub>3</sub> )CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Me	Cl	Me	H	
451	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	OMe	Me	Me	
452	benzyl	Cl	NO <sub>2</sub>	Cl	H	

Examples 453-471 given in TABLE 5 may be preferably prepared by treatment of compounds of formula (I, R<sup>3</sup> is OH or SH) with a base such as, but not limited to, potassium hydroxide in a solvent such as acetone or other inert solvent with a reagent R<sup>10</sup>-X where X is a leaving group (*vide supra*). These product compounds arise via the tautomeric nature of compounds of formula (I) where R<sup>3</sup> is OH or SH.

10

TABLE 5



Example	R <sup>1</sup>	R <sup>10</sup>	R <sup>3</sup>	mp °C
453	Me	H	2,4,6-trimethylphenyl	
454	Me	Me	2,4,6-trichlorophenyl	
455	Me	CH <sub>2</sub> cPr	4-chloro-2,6-dibromophenyl	
456	Me	COPh	2-bromo-4,6-dichlorophenyl	
457	Et	H	2,4,6-trimethylphenyl	
458	Et	Me	2,4,6-trichlorophenyl	
459	Et	Et	2,4,6-trichlorophenyl	
460	Et	i-Pr	2,4,6-trichlorophenyl	
461	Et	c-Pr	2,4,6-trichlorophenyl	
462	Et	n-Pr	2,4,6-trichlorophenyl	
463	Et	CH <sub>2</sub> cPr	2,4,6-trichlorophenyl	
464	Et	c-pentyl	2,4,6-trichlorophenyl	
465	Et	CH <sub>2</sub> cPr	4-chloro-2,6-dibromophenyl	
466	Et	COPh	2-bromo-4,6-dichlorophenyl	
467	Et	Me	2,4,6-trimethylphenyl	
468	Et	Me	4-chloro-2,6-dibromophenyl	
469	Et	Me	2-bromo-4,6-dichlorophenyl	
470	Ph	Me	2,4,6-trimethylphenyl	
471	Ph	CH <sub>2</sub> cPr	2,4,6-trichlorophenyl	

15

### Utility

#### CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

5

The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

10

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons. The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400  $\mu$ M hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately  $1 \times 10^8$  of the suspended cells were then centrifuged to form a pellet and frozen.

25

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM MgCl<sub>2</sub>, 2 mM EGTA, 1  $\mu$ g/l aprotinin, 1  $\mu$ g/ml leupeptin and 1  $\mu$ g/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet

30

rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is resuspended to a protein concentration of 360 µg/ml to be used in the assay.

- 5 Binding assays are performed in 96 well plates; each well having a 300 µl capacity. To each well is added 50 µl of test drug dilutions (final concentration of drugs range from  $10^{-10}$  -  $10^{-5}$  M), 100 µl of  $^{125}\text{I}$ -ovine-CRF ( $^{125}\text{I}$ -o-CRF) (final concentration 150 pM) and  
10 150 µl of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times  
15 with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

- Curves of the inhibition of  $^{125}\text{I}$ -o-CRF binding to cell membranes at various dilutions of test drug are  
20 analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (1980), which provides  $K_i$  values for inhibition which are then used to assess biological activity.

- A compound is considered to be active if it has a  
25  $K_i$  value of less than about 10000 nM for the inhibition of CRF.

#### Inhibition of CRF-Stimulated Adenylate Cyclase Activity

- 30 Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer



containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM  
MgCl<sub>2</sub>, 0.4 mM EGTA, 0.1% BSA, 1 mM  
isobutylmethylxanthine (IBMX), 250 units/ml  
phosphocreatine kinase, 5 mM creatine phosphate, 100  
5 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist  
peptides (concentration range 10<sup>-9</sup> to 10<sup>-6</sup>m) and 0.8  
mg original wet weight tissue (approximately 40-60 mg  
protein). Reactions are initiated by the addition of  
1 mM ATP/<sup>32</sup>P]ATP (approximately 2-4 mCi/tube) and  
10 terminated by the addition of 100 ml of 50 mM Tris-  
HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In  
order to monitor the recovery of cAMP, 1 µl of  
[<sup>3</sup>H]cAMP (approximately 40,000 dpm) is added to each  
tube prior to separation. The separation of [<sup>32</sup>P]cAMP  
15 from [<sup>32</sup>P]ATP is performed by sequential elution over  
Dowex and alumina columns.

#### In vivo Biological Assay

The *in vivo* activity of the compounds of the  
20 present invention can be assessed using any one of the  
biological assays available and accepted within the  
art. Illustrative of these tests include the Acoustic  
Startle Assay, the Stair Climbing Test, and the  
Chronic Administration Assay. These and other models  
25 useful for the testing of compounds of the present  
invention have been outlined in C.W. Berridge and A.J.  
Dunn *Brain Research Reviews* 15:71 (1990).  
Compounds may be tested in any species of rodent or  
small mammal.

30

Compounds of this invention have utility in the  
treatment of imbalances associated with abnormal  
levels of corticotropin releasing factor in patients  
suffering treating psychiatric disorders and  
35 neurological diseases including major depression,

anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be

present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral

solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in  
5 "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

10

#### Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg  
15 lactose, 50 mg cellulose, and 6 mg magnesium stearate.

#### Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is  
20 prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

25

#### Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of  
30 microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

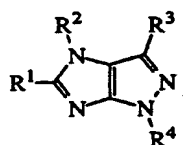
The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

- 5           Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments
- 10 described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

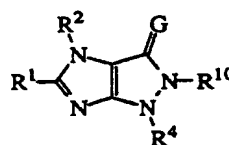
CLAIMS

WHAT IS CLAIMED IS:

- 5 1. A compound of Formulae (I) and (II):



(I)



(II)

- 10 isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof, wherein:

- 15  $R^1$  is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, where such haloalkyl is substituted with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>8</sub> cycloalkylalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, heteroaryl or heterocyclyl;

- 20  $R^2$  is C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, where each group can be optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, aryl, heteroaryl, heterocyclyl, halogen, cyano, NR<sup>6</sup>R<sup>7</sup>, OR<sup>7</sup>, thiol, S(O)<sub>n</sub>R<sup>9</sup>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, OC(O)R<sup>9</sup>, NR<sup>8</sup>COR<sup>7</sup>, NR<sup>8</sup>CONR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, CONR<sup>6</sup>R<sup>7</sup>;
- 25

- or  
S(O)<sub>n</sub>R<sup>9</sup>, COR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>;  
or  
C<sub>1</sub>-C<sub>4</sub> haloalkyl, where C<sub>1</sub>-C<sub>4</sub> haloalkyl may be  
5 substituted with 1-6 halogens;  
or  
aryl or aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl or  
heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl, or  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl), wherein C<sub>1</sub>-C<sub>4</sub> alkyl in  
10 aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl) or  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl) is optionally substituted  
with substituents selected from C<sub>1</sub>-C<sub>8</sub> alkyl, COR<sup>7</sup>,  
CO<sub>2</sub>R<sup>7</sup>, S(O)<sub>n</sub>R<sup>9</sup>, cyano and aryl;
- 15 n is independently at each occurrence 0, 1, or 2;
- R<sup>3</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-  
C<sub>6</sub> haloalkyl, where such haloalkyl is substituted  
with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>2</sub>-C<sub>10</sub>  
20 alkoxyalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, cyano, OR<sup>6</sup>, thiol,  
S(O)<sub>n</sub>R<sup>9</sup>, NR<sup>6</sup>R<sup>7</sup>, aryl, or heteroaryl;
- R<sup>4</sup> is phenyl, pyridyl, pyrimidyl, triazinyl, furanyl,  
naphthyl, quinolinyl, isoquinolinyl, thienyl,  
25 imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,  
benzofuranyl, benzothienyl, benzothiazolyl,  
isoxazolyl, 2,3-dihydrobenzofuranyl, 2,3-  
dihydrobenzothienyl, 1,2-benzopyranyl, 3,4-dihydro-  
1,2-benzopyranyl or pyrazolyl, where each R<sup>4</sup> is  
30 attached via an unsaturated carbon atom and each R<sup>4</sup>  
may be optionally substituted with 1 to 4 R<sup>5</sup>  
groups;

R<sup>5</sup> is independently at each occurrence selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, where C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl are optionally substituted with 1-3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>4</sub> alkyl, nitro, halogen, cyano, NR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>COR<sup>7</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, COR<sup>7</sup>, OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>CONR<sup>6</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, thiol, or S(O)<sub>n</sub>R<sup>9</sup>;  
or  
nitro, halogen, cyano, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens, NR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>COR<sup>7</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, COR<sup>7</sup>, OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>CONR<sup>6</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, thiol, or S(O)<sub>n</sub>R<sup>9</sup>;

R<sup>6</sup> and R<sup>7</sup> are independently at each occurrence selected from:  
(1) H;  
(2) C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>4</sub>-C<sub>12</sub> cycloalkylalkyl, each optionally substituted with 1-6 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl, cyano, nitro, OR<sup>12</sup>, thiol, S(O)<sub>n</sub>R<sup>9</sup>, COR<sup>12</sup>, CO<sub>2</sub>R<sup>12</sup>, NR<sup>8</sup>COR<sup>12</sup>, NR<sup>8</sup>CONR<sup>11</sup>R<sup>12</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, NR<sup>11</sup>R<sup>12</sup>, and CONR<sup>11</sup>R<sup>12</sup>;  
(3) aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl or heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl, or heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl);



- R<sup>8</sup> is independently at each occurrence selected from H,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or  
C<sub>4</sub>-C<sub>7</sub> cycloalkylalkyl;  
5 or  
phenyl or phenyl(C<sub>1</sub>-C<sub>4</sub> alkyl), each optionally  
substituted with 1-3 substituents selected from  
C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally  
substituted with 1-6 halogens, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH;  
10
- R<sup>9</sup> is independently at each occurrence selected from H,  
C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
C<sub>4</sub>-C<sub>7</sub> cycloalkylalkyl;  
or  
15 phenyl or phenyl(C<sub>1</sub>-C<sub>4</sub> alkyl), each optionally  
substituted with 1-3 substituents selected from  
C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally  
substituted with 1-6 halogens, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH;
- 20 R<sup>10</sup> is H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub>  
alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub>  
cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl),  
heteroaryl, heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl,  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl), where C<sub>1</sub>-C<sub>4</sub> haloalkyl is  
25 optionally substituted with 1 to 6 halogens;
- R<sup>11</sup> and R<sup>12</sup> are independently at each occurrence  
selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-  
C<sub>7</sub> cycloalkylalkyl, or C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally  
30 substituted with 1-6 halogens;  
or  
phenyl or phenyl(C<sub>1</sub>-C<sub>4</sub> alkyl), each optionally  
substituted with 1-3 substituents selected from

C1-C4 alkyl, halogen, C1-C4 haloalkyl optionally substituted with 1-6 halogens, C1-C4 alkoxy, OH;

5 aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R<sup>13</sup>;

10 heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, or indazolyl, each optionally substituted with 1 to 4  
15 substituents independently selected from at each occurrence R<sup>13</sup>;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 3  
20 substituents independently selected at each occurrence from R<sup>13</sup>;

R<sup>13</sup> is independently at each occurrence selected from  
25 C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C6 cycloalkyl, C4-C12 cycloalkylalkyl, where C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C6 cycloalkyl, C4-C12 cycloalkylalkyl are optionally substituted with 1-3 substituents independently selected at each occurrence from C1-C4 alkyl,  
30 nitro, halogen, cyano, NR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>COR<sup>9</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, COR<sup>9</sup>, OR<sup>9</sup>, CONR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>CONR<sup>8</sup>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, thiol, or S(O)<sub>n</sub>R<sup>9</sup>  
or

nitro, halogen, cyano, C<sub>1</sub>-C<sub>4</sub> haloalkyl optionally substituted with 1-6 halogens, NR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>COR<sup>9</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>9</sup>, COR<sup>9</sup>, OR<sup>9</sup>, CONR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>CONR<sup>8</sup>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, thiol, or S(O)<sub>n</sub>R<sup>9</sup>;

5

2. A compound of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof wherein: R<sup>4</sup> is phenyl, pyridyl  
10 or pyrimidyl, each optionally substituted by 1 to 4 R<sup>5</sup> groups.

3. A compound of claim 2 and isomers thereof, stereoisomeric forms thereof, or mixtures of  
15 stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof wherein: R<sup>1</sup> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, where such haloalkyl is substituted with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or aryl.

20

4. A compound of claim 3 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof wherein: R<sup>1</sup> is selected from  
25 H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, where such haloalkyl is substituted with 1-6 halogens, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or aryl and R<sup>4</sup> is phenyl, pyridyl or pyrimidyl, each optionally substituted by 1 to 4 R<sup>5</sup> groups.

30 5. A compound of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, selected from the group

- 1- (2-chloro-4-trifluoromethyl) phenyl-5-ethyl-3-methyl-4-  
[1- (1-methyl) butane] imidazo[4,5-c] pyrazole;
- 5 1- (2-chloro-4-trifluoromethyl) phenyl-5-ethyl-4- [1- (1-  
ethyl) butane] -3-methylimidazo[4,5-c] pyrazole;
- 4- (n-butyl) -1- (2-chloro-4-bromo) phenyl-5-ethyl-3-  
methylimidazo[4,5-c] pyrazole;
- 10 1- (2-chloro-4-bromo) phenyl-5-ethyl-3-methyl-4- [1- (1-  
methyl) butane] imidazo[4,5-c] pyrazole;
- 1- (2-chloro-4-bromo) phenyl-5-ethyl-4- [1- (1-  
15 ethyl) butane] -3-methylimidazo[4,5-c] pyrazole;
- 5-ethyl-3-fluoromethyl-4- [1- (1-methyl) butane] -1- (2,4,6-  
trichloro) phenylimidazo[4,5-c] pyrazole;
- 20 5-ethyl-4- [1- (1-methyl) butane] -1- (2,4,6-  
trichloro) phenylimidazo[4,5-c] pyrazole;
- 1- (2,6-dichloro-4-bromo) phenyl-5-ethyl-4- [1- (1-  
ethyl) butane] -3-methylimidazo[4,5-c] pyrazole;
- 25 1- (2,4-dichloro) phenyl-5-ethyl-4- [1- (1-ethyl) butane] -3-  
methylimidazo[4,5-c] pyrazole;
- 1- (2,4-dichloro) phenyl-5-ethyl-3-methyl-4- [1- (1-  
30 methyl) butane] imidazo[4,5-c] pyrazole;
- 1- (2,4-dichloro) phenyl-5-ethyl-3-methyl-4- [1- (1,3-  
dimethyl) butane] imidazo[4,5-c] pyrazole;
- 35 1- (2,6-dichloro-4-bromo) phenyl-5-ethyl-3-methyl-4- [1- (1-  
methyl) butane] imidazo[4,5-c] pyrazole;

- 5-ethyl-4-[1-(1-ethyl)butane]-3-methyl-1-(2,4,5-trichloro)phenylimidazo[4,5-c]pyrazole;
- 5 5-ethyl-3-methyl-4-[1-(1-methyl)butane]-1-(2,4,5-trichloro)phenylimidazo[4,5-c]pyrazole;
- 5-ethyl-4-[1-(1-methyl)pentane]-3-methyl-1-(2,4,6-trichloro)phenylimidazo[4,5-c]pyrazole;
- 10 1-(2-bromo-4-isopropyl)phenyl-5-ethyl-4-[1-(1-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;
- 15 1-(2-bromo-4-isopropyl)phenyl-5-ethyl-3-methyl-4-[1-(1-methyl)butane]imidazo[4,5-c]pyrazole;
- 1-(2-bromo-4,6-dichloro)phenyl-5-ethyl-4-[1-(1-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;
- 20 1-(2-bromo-4,6-dichloro)phenyl-5-ethyl-3-methyl-4-[1-(1-methyl)butane]imidazo[4,5-c]pyrazole;
- 4-(n-butyl)-1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-3-methylimidazo[4,5-c]pyrazole;
- 25 1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-3-methyl-4-[1-(3-methyl)butane]imidazo[4,5-c]pyrazole;
- 1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-4-[1-(2-ethyl)butane]-3-methylimidazo[4,5-c]pyrazole;
- 30 4-benzyl-1-(2,6-dichloro-4-bromo)phenyl-5-ethyl-3-methylimidazo[4,5-c]pyrazole; and
- 35 1-(2,6-dichloro-4-bromo)phenyl-4-(3,4-difluorobenzyl)-5-ethyl-3-methylimidazo[4,5-c]pyrazole.

6. A pharmaceutical composition comprising a  
pharmaceutically acceptable carrier and a  
therapeutically effective amount of a compound of claims  
5 1, 2, 3, 4 or 5.

7. A method of treating affective disorder, anxiety,  
depression, headache, irritable bowel syndrome, post-  
traumatic stress disorder, supranuclear palsy, immune  
10 suppression, Alzheimer's disease, gastrointestinal  
diseases, anorexia nervosa or other feeding disorder,  
drug addiction, drug or alcohol withdrawal symptoms,  
inflammatory diseases, cardiovascular or heart-related  
diseases, fertility problems, human immunodeficiency  
15 virus infections, hemorrhagic stress, obesity,  
infertility, head and spinal cord traumas, epilepsy,  
stroke, ulcers, amyotrophic lateral sclerosis,  
hypoglycemia or a disorder the treatment of which can  
be effected or facilitated by antagonizing CRF,  
20 including but not limited to disorders induced or  
facilitated by CRF, in mammals, comprising:  
administering to the mammal a therapeutically  
effective amount of a compound of claims 1, 2, 3, 4 or  
5.

25

# INTERNATIONAL SEARCH REPORT

I. International Application No  
PCT/US 98/17049

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 A61K31/415 //(C07D487/04,235:00,231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 190 457 A (CAMILO CORVI) 13 August 1986 see claim 1 -----	1,6,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 November 1998

Date of mailing of the international search report

02/12/1998

Name and mailing address of the ISA

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Alfaro Faus, I

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/17049

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 7  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/17049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 190457 A	13-08-1986	JP 61183288 A	15-08-1986